Proposed Rules

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This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 864

[Docket No. FDA–2025–N–1243]

Hematology and Pathology Devices; Reclassification of In Situ Hybridization Test Systems for Use With a Corresponding Approved Oncology Therapeutic Product

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed amendment; proposed order; request for comments.

SUMMARY: The Food and Drug Administration (FDA) is proposing to reclassify in situ hybridization (ISH) test systems indicated for use with a corresponding approved oncology therapeutic product (product codes NYQ, MVD, OWE, and PNK) from class III (premarket approval) into class II (special controls), subject to premarket notification. FDA is also proposing a new device classification regulation, along with the special controls that FDA believes are necessary to provide a reasonable assurance of safety and effectiveness for this device type.

DATES: Either electronic or written comments on the proposed order must be submitted by August 11, 2025. Please see section X of this document for the proposed effective date when the new requirements apply and for the proposed effective date of a final order based on this proposed order.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of August 11, 2025. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal Rulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand Delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2025–N–1243 for ''Hematology and Pathology Devices; Reclassification of In Situ Hybridization Test Systems for Use with a Corresponding Approved Oncology Therapeutic Product.'' Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday Eastern Time, 240–402–7500.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents, the plain language summary of the proposed order of not more than 100 words consistent with the ''Providing Accountability Through Transparency Act,'' or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

FOR FURTHER INFORMATION CONTACT: Soma Ghosh, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 3316, Silver Spring, MD 20993, 240–402–5333, *Soma.Ghosh@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background—Regulatory Authorities

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended, establishes a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) establishes three classes of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three classes of devices are class I (general controls), class II (general controls and special controls), and class III (general controls and premarket approval).

Section 513(a)(1) of the FD&C Act defines the three classes of devices. Class I devices are those devices for which the general controls of the FD&C Act (controls authorized by or under sections 501, 502, 510, 516, 518, 519, or 520 (21 U.S.C. 351, 352, 360, 360f, 360h, 360i, or 360j) or any combination of such sections) are sufficient to provide reasonable assurance of safety and effectiveness of the device; or those devices for which insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of safety and effectiveness or to establish special controls to provide such assurance, but because the devices are not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, and do not present a potential unreasonable risk of illness or injury, are to be regulated by general controls (section 513(a)(1)(A) of the FD&C Act).

Class II devices are those devices for which general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, but for which there is sufficient information to establish special controls to provide such assurance, including the issuance of performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines, recommendations, and other appropriate actions the Agency deems necessary to provide such assurance (section 513(a)(1)(B) of the FD&C Act).

Class III devices are those devices for which insufficient information exists to determine that general controls and special controls would provide a reasonable assurance of safety and effectiveness, and are purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury (section 513(a)(1)(C) of the FD&C Act).

Devices that were not introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976 (generally referred to as ''postamendments devices'') are classified automatically by section 513(f)(1) of the FD&C Act into class III without any action taken by FDA (Agency or we). Those devices remain in class III and require approval of a premarket approval application (PMA), unless and until: (1) FDA reclassifies the device into class I or II, or (2) FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of the premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807, subpart E, of the regulations (21 CFR part 807).

A postamendments device that has initially been classified into class III under section 513(f)(1) of the FD&C Act may be reclassified into class I or class II under section 513(f)(3) of the FD&C Act. Section 513(f)(3) of the FD&C Act provides that FDA, acting by administrative order, can reclassify the device into class I or class II on its own initiative, or in response to a petition from the manufacturer or importer of the device. To change the classification of the device, the proposed new class must have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use.[1]

FDA relies upon ''valid scientific evidence'' as defined in section 513(a)(3) of the FD&C Act and 21 CFR 860.7(c)(2), in the classification process to determine the level of regulation for devices.[2] In general, to be considered in the reclassification process, the ''valid scientific evidence'' upon which the Agency relies must be publicly available (see section 520(c) of the FD&C Act (21 U.S.C. 360j(c))). Publicly available information excludes trade secret and/or confidential commercial information, *e.g.,* the contents of a pending PMA (see section 520(c) of the FD&C Act). Section 520(h)(4) of the FD&C Act provides that FDA may use, for reclassification of a device, certain information in a PMA 6 years after the application has been approved. This includes information from clinical and preclinical tests or studies that demonstrate the safety and effectiveness of the device, but it does not include the descriptions of methods of manufacture and product composition and other trade secrets.

In accordance with section 513(f)(3) of the FD&C Act, FDA is issuing this proposed order to reclassify postamendments class III ISH-based test systems indicated for use with a corresponding approved oncology therapeutic product (product codes NYQ, MVD, OWE, and PNK),[3] hereafter collectively referred to as oncology therapeutic ISH-based test systems, into class II (special controls) subject to premarket notification under a new device classification regulation with the name ''In Situ Hybridization Test Systems Indicated for Use with a Corresponding Approved Oncology Therapeutic Product.''

Oncology therapeutic ISH-based test systems, currently designated under product codes NYQ, MVD, OWE, and PNK, are prescription in vitro diagnostic (IVD) devices that utilize ISH technology to qualitatively or quantitatively detect specific nucleic acid sequences in human specimens and are indicated for use with a corresponding approved oncology therapeutic product. These test systems include companion diagnostic (CDx) devices, which are devices that provide information that is essential for the safe and effective use of a corresponding approved therapeutic product and the use of which is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product (Ref. 1). Although the devices within the different product codes have distinct characteristics in certain respects—for example, each product code generally represents devices with a distinct ISH technique, specific biomarker(s) detected by the test system, specimen type(s) tested, and/or specific FDA approved therapeutic product(s) for which the device is indicated for use—FDA has determined that these devices have the same or a similar risk profile and sufficiently similar purposes, designs, functions, and other features related to safety and effectiveness such that the same regulatory controls are necessary and sufficient to provide reasonable assurance of safety and effectiveness. For these reasons and considering that FDA did not identify

[1] See generally section 513 of the FD&C Act.

[2] See generally *id.*

[3] FDA's Center for Devices and Radiological Health (CDRH) uses product codes to help categorize and assure consistent regulation of medical devices. A product code consists of three characters that are assigned at the time a product code is generated and is unique to a product type. The three characters carry no other significance and are not an abbreviation.

any unique risks associated with the distinctions across these devices, FDA is proposing a single classification regulation to classify all oncology therapeutic ISH-based test systems into class II. Previously approved devices remain under their respective product codes (*i.e.,* NYQ, MVD, OWE, or PNK) and future oncology therapeutic ISH-based test systems would either be assigned to one of the currently existing product codes or a new product code, as appropriate. The new classification regulation would classify oncology therapeutic ISH-based test systems, currently designated under product codes NYQ, MVD, OWE, and PNK, as well as future oncology therapeutic ISH-based test systems.

Based upon the extensive PMA data available to FDA in accordance with section 520(h)(4) of the FD&C Act,[4] [5] published peer-reviewed literature studying this longstanding and well-understood technology, and data available to the Agency demonstrating a lack of significant postmarket safety signals, FDA believes there is sufficient information to reclassify these devices from class III (premarket approval) into class II (special controls). FDA believes the standard in section 513(a)(1)(B) of the FD&C Act is met as there is sufficient information to establish special controls, which, in addition to general controls, would provide reasonable assurance of the safety and effectiveness of these devices.[6]

Therefore, FDA is proposing to establish a new device classification regulation, ''In Situ Hybridization Test Systems for Use with a Corresponding Approved Oncology Therapeutic Product,'' and classify this device type into class II along with the special controls that the Agency believes are necessary to provide a reasonable assurance of the safety and effectiveness for these devices.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. FDA has determined that premarket notification is necessary to provide a reasonable assurance of the safety and effectiveness of oncology therapeutic ISH-based test systems, therefore, the Agency does not intend to exempt these proposed class II devices from the premarket notification (510(k)) submission requirement as provided under section 510(m) of the FD&C Act.[7] If this proposed order is finalized, persons who intend to market this type of device must submit to FDA a premarket notification under section 510(k) of the FD&C Act prior to marketing the device.

II. Regulatory History of the Devices

In accordance with section 513(f)(1) of the FD&C Act, oncology therapeutic ISH-based test systems were automatically classified into class III because they were not introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, and have not been found substantially equivalent to a device placed in commercial distribution after May 28, 1976, which was subsequently classified or reclassified into class I or class II. Therefore, these devices are subject to the PMA requirements under section 515 of the FD&C Act (21 U.S.C. 360e).

On December 31, 2001, FDA approved, through a panel-track supplement[8] to an original PMA, the first oncology therapeutic ISH-based test system, a CDx device, PathVysion HER-2 DNA Probe Kit (P980024/S001) (product code MVD), designed to detect amplification of the HER-2/neu gene via fluorescence ISH (FISH) in formalin-fixed paraffin-embedded (FFPE) human breast cancer tissue for use as an aid in the assessment of patients for whom trastuzumab is being considered (Ref. 2). In a November 6, 2002, **Federal Register** notice (67 FR 67629), FDA announced the approval order and the availability of the Summary of Safety and Effectiveness Data (SSED) for the device.

Since the first approval order for an oncology therapeutic ISH-based test system, FDA has reviewed and approved 7 original PMAs and approximately 130 PMA supplements for oncology therapeutic ISH-based test systems under product codes NYQ, MVD, OWE, and PNK.[9] In accordance with the ''six-year rule'' described in section 520(h)(4) of the FD&C Act (21 U.S.C. 360j(h)(4)) (Ref. 3), FDA considered data contained in the following 6 original PMAs and 1 panel-track supplement to an original PMA, representing devices from all 4 product codes (*i.e.,* NYQ, MVD, OWE, and PNK) for oncology therapeutic ISH-based test systems: PathVysion HER-2 DNA Probe Kit (P980024/S001) (product code MVD) (Ref. 2), DakoCytomation HER2 FISH pharmDX Kit (P040005) (product code MVD) (Ref. 4), SPOT-Light HER2 CISH Kit (P050040) (product code NYQ) (Ref. 5), HER2 CISH pharmDx Kit (P100024) (product code NYQ) (Ref. 6), INFORM HER2 Dual ISH DNA Probe Cocktail (P100027) (product code NYQ) (Ref. 7), Vysis ALK Break Apart FISH Probe Kit (P110012) (product code OWE) (Ref. 8), and Vysis CLL FISH Probe Kit (P150041) (product code PNK) (Ref. 9). As of August 30, 2024, fewer than 6 years have passed since FDA's approval

[4] In proposing to reclassify oncology therapeutic ISH-based test systems from class III to class II, FDA, on its own initiative, relied on data from relevant PMAs and a relevant PMA panel-track supplement, available to FDA with product codes of NYQ, MVD, OWE, and PNK, in accordance with the six-year rule (see section 520(h)(4) of the FD&C Act (21 U.S.C. 360j(h)(4))) (see also, FDA's guidance ''Guidance on Section 216 of the Food and Drug Administration Modernization Act of 1997—Guidance for Industry and for FDA Reviewers | FDA''). This data was from relevant PMAs and a PMA panel-track supplement approved after November 28, 1990, and before August 30, 2018, for this specific proposed reclassification as noted in section II of this proposed order. See also, FDA's premarket approval database, available at *https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm.*

[5] For the purpose of this proposed order, PMA data considered in accordance with section 520(h)(4) includes only that data which was submitted to and therefore considered by FDA at the time the PMA was reviewed and approval was issued.

[6] FDA notes that the ''ACTION'' caption for this proposed order is styled as ''Proposed amendment; proposed order; request for comments'' rather than ''Proposed order.'' Beginning in December 2019, this editorial change was made to indicate that the document ''amends'' the Code of Federal Regulations. The change was made in accordance with the Office of the Federal Register's (OFR) interpretations of the Federal Register Act (44 U.S.C. chapter 15), its implementing regulations (1 CFR 5.9 and parts 21 and 22), and the Document Drafting Handbook.

[7] In considering whether to exempt class II devices from premarket notification, FDA considers whether premarket notification for the type of device is necessary to provide reasonable assurance of safety and effectiveness of the device. FDA generally considers the factors initially identified in the January 21, 1998 **Federal Register** notice (63 FR 3142) and further explained in FDA's guidance issued on February 19, 1998, entitled ''Procedures for Class II Device Exemptions from Premarket Notification, Guidance for Industry and CDRH Staff'' in determining whether premarket notification is necessary for class II devices. FDA also considers that, even when exempting devices from the 510(k) requirements, these devices would still be subject to certain limitations on exemptions, for example, the general limitations set forth in 21 CFR 864.9.

[8] The term ''panel-track supplement'' is defined in section 737(4)(B) of the FD&C Act as, ''a supplement to an approved premarket application or premarket report under section 515 that requests a significant change in design or performance of the device, or a new indication for use of the device, and for which substantial clinical data are necessary to provide a reasonable assurance of safety and effectiveness.''

[9] FDA has determined that the devices assigned to product codes NYQ, MVD, OWE, and PNK all utilize ISH-based technology for use with a corresponding approved oncology therapeutic product, have sufficiently similar purposes, designs, functions, and other features related to safety and effectiveness such that all oncology therapeutic ISH-based test systems have the same or a similar risk profile. Further, FDA has not identified any unique risks associated with the distinctions across these devices.

of the PMA and PMA supplements for VENTANA HER2 Dual ISH DNA Probe Cocktail (P190031) and several PMA supplements associated with the 7 identified PMAs. Therefore, no information from those documents has been used in support of this proposed order to reclassify oncology therapeutic ISH-based test systems into class II (see section 520(h)(4) of the FD&C Act (21 U.S.C. 360j(h)(4))).[10]

A review of data from FDA's Manufacturer and User Facility Device Experience (MAUDE) database, which contains Medical Device Reports (MDRs) of adverse events, indicates that as of July 12, 2024, there have been 14 reported events for oncology therapeutic ISH-based test systems under the product codes NYQ (N = 9 MDRs), OWE (N = 3 MDRs), and MVD (N = 2 MDRs) since the approval of the first oncology therapeutic ISH-based test system in 2001. There have been no MDRs reported under the product code PNK.

A significant majority (over 80 percent) of the MDRs reported under the product codes listed have identified no known impact or consequence to patient, no patient involvement, and/or no clinical signs, symptoms, or conditions. After review of the data, the Agency has determined that broken control slides account for the device problem associated with nearly one-third of the MDR reported events, with other reported device problems including, for example, communication or transmission problem, false negative result, false positive result, and device operates differently than expected.

A search of these product codes in FDA's Medical Device Recalls database indicates that as of July 12, 2024, there have been 3 class II recalls [11] and no class I or III recalls [12] involving oncology therapeutic ISH-based test systems. The class II recalls occurred between 2011 and 2016 and have since been terminated. The recalls were due to an incorrect probe concentration, weak red chromogenic signals, and possible fungal contamination of a reagent potentially leading to false test results. This postmarket data, coupled with the fact that none of the recalls and only 1 MDR were reported to have caused or led to patient harm, indicate a generally good safety record for these device types. These events reflect the risks to health identified in section V of this proposed order, which FDA believes can effectively be mitigated through general controls and the implementation of the special controls proposed herein.

[10] In accordance with section 520(h)(4) of the FD&C Act, FDA has not relied on information in PMAs and PMA supplements approved within the last 6 years to develop the proposed special controls or to otherwise inform this proposed reclassification action.

[11] The database searches initially identified 6 class II recalls. However, after manual review of the data it has been determined that 3 of the recalls were improperly reported. The 3 improperly reported class II recalls were instead related to device product codes that fall outside the scope of this proposed order. As such, for the purpose of this proposed order the data related to these recalls have been excluded from the Agency's postmarket surveillance analysis and discussion surrounding recall data.

[12] Class I, II, and III recalls are defined in 21 CFR 7.3(m).

III. Device Description

Oncology therapeutic ISH-based test systems are postamendments devices classified into class III under section 513(f)(1) of the FD&C Act. These oncology therapeutic ISH-based test systems are prescription IVDs intended for the qualitative or quantitative detection of specific nucleic acid sequences in human specimens using ISH technology, with either chemical- or fluorescent-labeled probes, through manual techniques, automated instrumentation, or a combination of manual techniques and automated instrumentation, and are indicated for use with a corresponding approved oncology therapeutic product. These ISH-based test systems include IVD CDx devices which are devices that provide information that is essential for the safe and effective use of a corresponding therapeutic product.[13] The use of an IVD CDx device with a therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, including the labeling of any generic equivalents of the therapeutic product.[14] An IVD CDx device could be essential for the safe and effective use of a corresponding therapeutic product to:

- Identify patients who are most likely to benefit from the therapeutic product;
- Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with the therapeutic product;
- Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (*e.g.,* schedule, dose, discontinuation) to achieve improved safety or effectiveness;
- Identify patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective, *i.e.,* there is insufficient information about the safety and effectiveness of the therapeutic product in any other population.

FDA does not include in this definition IVD devices that are not essential to the safe and effective use of a therapeutic product.[15] For more information on CDx devices, see FDA's guidance titled ''In Vitro Companion Diagnostic Devices—Guidance for Industry and Food and Drug Administration Staff'' (Ref. 1).

FDA proposes to revise 21 CFR part 864 to create a new device classification regulation with the name ''In Situ Hybridization Test Systems for Use with a Corresponding Approved Oncology Therapeutic Product.'' ISH test systems indicated for use with a corresponding approved oncology therapeutic product are identified as prescription IVD devices consisting of nucleic acid probes intended for the qualitative or quantitative detection of specific nucleic acid sequences in human clinical specimens to provide information related to the use of a corresponding approved oncology therapeutic product as described in the corresponding approved oncology therapeutic product labeling.

[13] FDA, ''In Vitro Companion Diagnostic Devices—Guidance for Industry and Food and Drug Administration Staff,'' August 6, 2014. Available at *https://www.fda.gov/media/81309/download.*

[14] *Id.*

IV. Proposed Reclassification and Summary of Reasons for Reclassification

In accordance with section 513(f)(3) of the FD&C Act and 21 CFR part 860, subpart C, FDA is proposing to reclassify oncology therapeutic ISH-based test systems from class III into class II, subject to premarket notification (510(k)) requirements. FDA believes that there is sufficient information to establish special controls, and that these special controls, together with general controls, would effectively mitigate the risks to health identified in section V and are necessary to provide a reasonable assurance of the safety and effectiveness of oncology therapeutic ISH-based test systems. Oncology therapeutic ISH-based test systems are prescription IVD devices, and under this proposed order, if finalized, they will be identified as such. Therefore, these devices are subject to the prescription labeling requirements for IVD products (see 21 CFR 809.10(a)(4) and (b)(5)(ii)).

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. For oncology therapeutic ISH-based test

[15] *Id.*

systems, FDA has determined that premarket notification is necessary to provide a reasonable assurance of the safety and effectiveness of these devices.[16] Therefore, the Agency does not intend to exempt these proposed class II devices from 510(k) requirements. If this proposed order is finalized, persons who intend to market an oncology therapeutic ISH-based test system will need to submit to FDA a 510(k) and receive clearance prior to marketing the device.

This proposed order, if finalized, will decrease regulatory burden on industry, as manufacturers will no longer have to submit a PMA for these types of devices but can instead submit a 510(k) to the Agency for review prior to marketing their device. The 510(k) pathway is less burdensome and generally more cost-effective for industry and FDA than the PMA pathway, the most stringent type of device marketing application required by FDA. A 510(k) typically results in a shorter premarket review timeline compared to a PMA, which ultimately may provide more timely access of these types of devices to patients. FDA expects that the reclassification of these devices would enable more manufacturers to develop these types of devices such that patients would benefit from increased access to appropriately safe and effective tests.

Additionally, manufacturers may wish to use predetermined change control plans (PCCPs) as a way to implement future modifications to their devices without needing to submit a new 510(k) for each significant change or modification [17] while continuing to provide a reasonable assurance of device safety and effectiveness.[18] FDA reviews a PCCP as part of a marketing submission for a device to ensure the continued safety and effectiveness of the device without necessitating additional marketing submissions for implementing each modification described in the PCCP. When used appropriately, PCCPs authorized by FDA are expected to be least burdensome for manufacturers and FDA.[19]

FDA believes that there is sufficient information available to FDA through the PathVysion HER-2 DNA Probe Kit (P980024/S001) PMA panel-track supplement and DakoCytomation HER2 FISH pharmDx Kit (P040005), SPOT-Light HER2 CISH Kit (P050040), HER2 CISH pharmDx Kit (P100024), INFORM HER2 Dual ISH DNA Probe Cocktail (P100027), Vysis ALK Break Apart FISH Probe Kit (P110012), and Vysis CLL FISH Probe Kit (P150041) PMAs [20] (Refs. 2 and 4–9), published peer-reviewed literature on ISH technology, and FDA's publicly available MAUDE and Medical Device Recalls databases to establish special controls that effectively mitigate the risks to health identified in section V. More specifically, in evaluating these data sources, FDA has identified the risks to health for inclusion in the overall risk assessment for oncology therapeutic ISH-based test systems. The Agency has considered the risks to health identified by these sources and used certain information from these sources in establishing special controls that include mitigation measures for each of the risks to health identified in section V. Accordingly, these devices should continue to demonstrate safety and effectiveness upon their reclassification from class III to class II when conformity with the special controls is demonstrated. Absent the special controls identified in this proposed order, general controls applicable to these devices are insufficient to provide reasonable assurance of the safety and effectiveness of oncology therapeutic ISH-based test systems.

V. Risks to Health

FDA is providing a substantive summary of the valid scientific evidence concerning the public health benefits of the use of oncology therapeutic ISH-based test systems, and the risks to health of these devices (see further discussion of the special controls being proposed to mitigate these risks in section VII of this proposed order). FDA considered data from 6 PMAs and 1 PMA panel-track supplement available to FDA under section 520(h)(4) of the FD&C Act, published peer-reviewed literature on ISH technology, and postmarket information regarding oncology therapeutic ISH-based test systems.

Cancer continues to be one of the two leading causes of death in the United States (Ref. 10). Biomarker tests for molecularly targeted cancer therapies aim to provide information for health care providers to target and/or tailor cancer treatment based on identifiable molecular differences between patients, with the goal of improving patient outcomes while minimizing risks related to treatment side effects. Oncology therapeutic ISH-based test systems provide a benefit to the public health by aiding in oncology therapeutic product treatment decisions. These test systems may provide information that is essential for the safe and effective use of a corresponding approved therapeutic product. For example, health care providers may use a relevant oncology therapeutic ISH-based test system to select the appropriate therapy for a patient or to monitor a particular patient's response to an approved oncology therapeutic product for the purpose of optimizing a dosing regimen. These devices can be used to enable personalization of oncology care by identifying patients who are most likely to benefit from a specific therapy and yield improved clinical outcomes, or who are at varying degrees of risk for a particular side effect related to the use of a specific therapy. Ultimately, the use of these devices informs treatment decisions and has a significant public health impact for cancer patients.

The Agency has identified the following risks to health associated with the use of oncology therapeutic ISH-based test systems:

- *False negative test results or false positive test results.* False negative test results or false positive test results may negatively influence oncology therapeutic product treatment decisions for cancer patients. For example, false positive test results may result in the withholding of appropriate oncology therapeutic treatment, delayed treatment from an available appropriate alternative therapy, or receiving inappropriate therapy with varying degrees of consequence (*e.g.,* failing to adjust therapy to achieve optimal clinical outcome or exposing a patient to otherwise avoidable serious adverse health risks caused by the therapeutic product).
- *Failure of the test system to perform as intended or indicated.* Failure of the test system to perform as intended or indicated may result in inappropriate

[16] See *supra* note 8.

[17] For the purpose of this proposed order reference to ''modification'' means a significant change or modification that would generally require a new premarket notification under 21 CFR 807.81(a)(3).

[18] Section 3308 of the Food and Drug Omnibus Reform Act of 2022, Title III of Division FF of the Consolidated Appropriations Act, 2023, Public Law. 117–328 (''FDORA''), enacted on December 29, 2022, added section 515C ''Predetermined Change Control Plans for Devices'' to the FD&C Act. Section 515C has provisions regarding predetermined change control plans (PCCPs) for devices requiring premarket approval or premarket notification. Under section 515C, supplemental applications (section 515C(a)) and new premarket notifications (section 515C(b)) are not required for a change to a device that would otherwise require a premarket approval supplement or new premarket notification if the change is consistent with a PCCP approved or cleared by FDA.

[19] Sections 513 and 515 of the FD&C Act. See also, FDA's guidance ''The Least Burdensome Provisions: Concept and Principles | FDA.''

[20] In accordance with section 520(h)(4) of the FD&C Act, FDA has not relied on information in PMAs and PMA supplements approved within the last 6 years to develop the proposed special controls or to otherwise inform this proposed reclassification action.

clinical management, due to, among other things, the potential need to rerun the test, leading to a delay in effective treatment or inappropriate treatment for a patient based on delayed results that are essential for the safe and effective use of a corresponding therapeutic product.

- *Failure to correctly interpret test results.* Failure to correctly interpret test results, such as, incorrect interpretation/reading of the stained slides, may result in the same negative outcomes associated with false negative or false positive test results as previously discussed. For example, incorrectly interpreting the test results as positive (*i.e.,* false positive) may lead to a patient receiving ineffective or unnecessary treatment that may unnecessarily expose them to treatment toxicities.

VI. Summary of Data Upon Which the Reclassification Is Based

The safety and effectiveness of this device type has become well established since the initial approval of the first oncology therapeutic ISH-based test system in 2001. FDA believes that oncology therapeutic ISH-based test systems should be reclassified from class III (premarket approval) into class II (special controls) because special controls can be established to mitigate the risks to health identified in section V and, in addition to general controls, provide a reasonable assurance of the safety and effectiveness of these devices. The proposed special controls are identified by FDA in section VII of this proposed order.

Taking into account the health benefits of the use of these devices and the nature and known incidence of the risks to health of the devices, FDA on its own initiative is proposing to reclassify these postamendments class III devices into class II. FDA believes, that when used as indicated, oncology therapeutic ISH-based test systems can provide significant benefits to health care providers and patients.

In proposing to reclassify and establish special controls for oncology therapeutic ISH-based test systems, FDA has considered and analyzed the following information: (1) data from 6 PMAs and 1 PMA panel-track supplement for oncology therapeutic ISH-based test systems available to FDA in accordance with section 520(h)(4) of the FD&C Act, (2) published peer-reviewed literature on ISH technology, and (3) MDR and recall data from the Agency's publicly available MAUDE and Medical Device Recalls databases. The available evidence demonstrates that there are public health benefits derived from the use of oncology therapeutic ISH-based test systems which provide information related to the use of a corresponding approved oncology therapeutic product, such as information that is essential for the safe and effective use of a corresponding approved oncology therapeutic product. In addition, the nature of the associated risks to health are known, and special controls can be established to sufficiently mitigate these risks.

FDA considered the safety and effectiveness of oncology therapeutic ISH-based test systems through review of PMA data going back to the initial approval of the first oncology therapeutic ISH-based test system in 2001, under product code MVD (Ref. 2). Subsequently, between 2005 and 2020, FDA approved 7 PMAs for oncology therapeutic ISH-based test systems under the product codes NYQ, MVD, PNK, and OWE. For the purpose of this reclassification, of the 7 original PMAs and 1 PMA panel-track supplement that the Agency has approved for oncology therapeutic ISH-based test systems, FDA was able to consider data from the following 6 original PMAs and 1 panel-track supplement to an original PMA in accordance with section 520(h)(4) of the FD&C Act: PathVysion HER-2 DNA Probe Kit (P980024/S001), DakoCytomation HER2 FISH pharmDx Kit (P040005), SPOT-Light HER2 CISH Kit (P050040), HER2 CISH pharmDx Kit (P100024), INFORM HER2 Dual ISH DNA Probe Cocktail (P100027), Vysis ALK Break Apart FISH Probe Kit (P110012), and Vysis CLL FISH Probe Kit (P150041) (Ref. 2 and 4–9).[21]

As part of the Agency's analysis in proposing to reclassify oncology therapeutic ISH-based test systems, FDA reviewed and considered information provided within each of these applications, to include information available in the SSEDs and device labeling for each application, which demonstrated a reasonable assurance of safety and effectiveness for the devices. The Agency considered the analytical and clinical studies performed and device performance data demonstrating appropriate performance of the device, which supported each approval, when developing the proposed special controls which FDA believes can effectively mitigate those risks to health identified in section V and can provide a reasonable assurance of the safety and effectiveness for oncology therapeutic ISH-based test systems. Additionally, FDA identified the potential adverse effects or risks to health of the devices based on information provided within the applications, to be false test results (*i.e.,* false positive and false negative test results), failure to correctly interpret test results, and failure of the test system to perform as intended or indicated. Based on data collected in the corresponding clinical studies submitted in support of the approvals and given that oncology therapeutic ISH-based test systems are diagnostic devices, the adverse event profile for these devices was generally deemed acceptable as there were no direct adverse effects or additional safety hazards to the patients being tested beyond routine procedures performed for a cancer diagnosis.

While the devices that are the subject of the 6 PMAs and 1 PMA panel-track supplement have unique device attributes in certain respects (*e.g.,* specific ISH technique utilized, specific biomarker(s) detected by the test system, specimen type(s), and/or specific FDA approved therapeutic product(s) for which the device is indicated for use), FDA has determined that these devices have sufficiently similar purposes, designs, functions, and other features related to safety and effectiveness such that the information and data reviewed and analysis conducted by FDA was analogous across all 7 applications available to the Agency in accordance with section 520(h)(4) of the FD&C Act. As such, and in order to avoid redundancy, the following two summaries are intended to provide examples that are representative of the PMA information and data that was reviewed and considered by FDA across the 7 applications in proposing to reclassify oncology therapeutic ISH-based test systems from class III (premarket approval) into class II (special controls).

On December 31, 2001, FDA approved, through a panel-track supplement to an original PMA, the first oncology therapeutic ISH-based test system, a CDx device, PathVysion HER-2 DNA Probe Kit with an intended use to detect amplification of the HER-2/neu gene via FISH in FFPE human breast cancer tissue specimens and for use as an aid in the assessment of patients for whom trastuzumab is being considered (product code MVD) (P980024/S001) (Ref. 2). The Agency considered the submitted studies and data in the approved submission, which demonstrated that the PathVysion HER-2 DNA Probe Kit has acceptable performance on FFPE human breast

[21] As previously noted, as of August 30, 2024, fewer than 6 years have passed since FDA's approval of the PMA and PMA supplements for VENTANA HER2 Dual ISH DNA Probe Cocktail (P190031). Therefore, no information from those documents has been used in support of this proposed order to reclassify oncology therapeutic ISH-based test systems into class II (see section 520(h)(4) of the FD&C Act (21 U.S.C. 360j(h)(4))).

cancer tissue sections with varying levels of gene amplification. Such studies include clinical studies demonstrating that the PathVysion HER-2 DNA Probe Kit, when compared to the reference methods immunohistochemistry (IHC) and clinical trial assay (CTA), has similar ability to detect HER-2/neu amplification in specimens from patients with stage II, node positive breast cancer. Potential adverse effects of the device include the identified risks of false positive or false negative test results and the misassignment of patients to receive a more aggressive therapy with the potential exposure to serious side effects or excluding a patient from receiving a therapy for which they might benefit. FDA's review of the PMA panel-track supplement determined that the rate of false positivity and false negativity are within acceptable limits compared to the reference methods and the data generated from these studies was sufficient to demonstrate a reasonable assurance of the safety and effectiveness of this device when used as intended. Beyond the risk of false positive or false negative test results, the PathVysion HER-2/neu DNA Probe assay involves testing on FFPE human breast cancer tissue sections for which such procedures are routinely performed for breast cancer diagnosis. The test, therefore, presents no additional safety hazard to the patient being tested.

Additionally, on August 26, 2011, FDA approved P110012, for the Vysis ALK Break Apart FISH Probe Kit PMA (product code OWE) (Ref. 8). The Vysis ALK Break Apart FISH Probe Kit test system is a qualitative test intended to detect rearrangements involving the ALK gene via FISH in FFPE non-small cell lung cancer (NSCLC) tissue specimens to aid in identifying patients eligible for treatment with Xalkorie (crizotinib). Analytical and clinical data provided in this PMA supported that there is reasonable assurance of safety and effectiveness of this device for use in the assessment of ALK gene rearrangements (*e.g.,* translocations, inversions, and deletions) and is sufficient to effectively identify appropriate patients to be considered for crizotinib therapy. These data included the results of a clinical trial (referred to as Study 1005 in the SSED), which met its primary effectiveness endpoint of having an objective response rate (ORR) as assessed by the investigator on a response-evaluable population using Response Evaluation Criteria in Solid Tumors (RECIST) v 1.0 with 95 percent confidence intervals (CI) [ORR of 50 percent (95 percent CI: 42, 59)]. The response rate data from this study was used to support the accelerated approval of crizotinib and a reasonable assurance of safety and effectiveness of the Vysis ALK Break Apart FISH Probe Kit with regards to identifying ALK gene rearrangements in the tumors of patients with previously treated, advanced (locally or metastatic) NSCLC, for whom crizotinib is being considered. Potential adverse effects of the Vysis ALK Break Apart FISH Probe Kit include failure of the device to perform as intended or indicated, failure to correctly interpret test results, and/or false positive test results or false negative test results that could lead to improper patient management decisions regarding cancer treatment. Conclusions drawn from non-clinical and clinical studies indicated overall acceptable performance including accuracy and reproducibility demonstrating that the device is reasonably safe and effective for its intended use. Further, the potential adverse effects of the device are also based on data collected in the clinical study conducted to support the PMA approval. As a diagnostic test, the Vysis ALK Break Apart FISH Probe Kit involved testing on FFPE human NSCLC cancer tissue sections for which these tissue sections are routinely removed for NSCLC cancer diagnosis. Therefore, no additional safety hazard was reported for the patients being tested.

In addition to PMA data from the 6 available PMAs and 1 PMA panel-track supplement, FDA considered that ISH is a well-established technology and it has been commonly used in both research and clinical settings for decades and at this time its general principles are well understood and widely published in the literature. Over the past five decades, there have been significant scientific developments aimed at addressing certain ISH limitations and expanding the applications of the technology, such as the emergence of non-radioactive labeled probes and FISH technique. These developments further demonstrate the maturity of this technology (Refs. 11–14). FDA considered the breadth of knowledge available regarding ISH as an established technology in proposing to reclassify oncology therapeutic ISH-based test systems from class III into class II. This includes, for example, the establishment of special controls that FDA believes can effectively mitigate those identified risks to health (discussed in section V) and can ensure a reasonable assurance of the safety and effectiveness for these devices.

Finally, a search of FDA's publicly available MAUDE database revealed 14 reported events for oncology therapeutic ISH-based test systems under the product codes NYQ, OWE, and MVD. There have been no MDRs reported under product code PNK. A search of FDA's publicly available recall database revealed no entries for devices under the MVD, OWE, and PNK product codes. Notably, only 1 MDR reportedly caused or led to patient harm. There have been three class II recalls involving oncology therapeutic ISH-based test systems under the NYQ product code; however, none of the recalls were determined to have caused or led to patient harm. This postmarket data demonstrating a low number of reported events indicate a generally good safety record for these device types (see further discussion of the MDR and recall data in section II of this proposed order).

Based on the Agency's review of the information described in this proposed order, FDA has determined that special controls, in addition to general controls, are necessary to provide a reasonable assurance of safety and effectiveness for these devices, and that sufficient information exists to establish such special controls. Therefore, FDA, on its own initiative, is proposing to reclassify oncology therapeutic ISH-based test systems from class III (premarket approval) into class II (special controls) subject to premarket notification (510(k)) requirements.

VII. Proposed Special Controls

FDA believes that the following proposed special controls would mitigate each of the risks to health described in section V and that these special controls, in addition to general controls, would provide a reasonable assurance of safety and effectiveness for oncology therapeutic ISH-based test systems.

Risks of false negative test results or false positive test results, failure of the test system to perform as intended or indicated, and failure to correctly interpret test results (caused by, for example, failure of the probes, instruments or software, to perform as expected or failure of the intended user to correctly perform the test) can be mitigated by special controls, including certain design verification and validation activities (for example, documentation of such activities), as well as certain labeling requirements. Examples of verification and validation information to be included in the design of the devices includes, for example, documentation of clinical data demonstrating acceptable performance of the device for its intended use based on data generated using a dataset representative of the intended use

population. Non-clinical performance testing must include specification of the criteria for test result interpretation and reporting and supporting validation of the device's cut-off(s) or clinical decision threshold(s). In addition, device design verification and validation information must include the specifications for risk mitigation elements intended to mitigate risks associated with testing and results interpretation, including controls, procedures, and user training requirements.

Risks of false negative test results and false positive test results and failure to correctly interpret test results can be further mitigated by special controls that require specific information in the labeling for these test systems. For example, specific required limiting statement(s) can aid in mitigating the risk of incorrect interpretation/reading of the stained slides leading to false test results. The risk of failure of the test system to perform as intended or indicated can be mitigated by labeling special controls that require an appropriate, as determined by FDA, summary of the performance studies performed and the results of those studies, thus informing the user of the expected performance of the device. Table 1 shows how FDA believes such risks to health described in section V would be mitigated by the proposed special controls.

TABLE 1—RISKS TO HEALTH AND MITIGATION MEASURES FOR ONCOLOGY THERAPEUTIC ISH-BASED TEST SYSTEMS

Identified risks to health	Mitigation measures
False negative test results or false positive test results.	Certain design verification and validation activities, including certain analytical validation and clinical validation data. Certain labeling information, including certain limiting statement(s) and 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 limiting statement(s), and 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 limiting statement(s), and certain performance information.

If this proposed order is finalized, oncology therapeutic ISH-based test systems will be identified as prescription IVD devices. Therefore, these devices would continue to be subject to the prescription labeling requirements for IVD products (see 21 CFR 809.10(a)(4) and (b)(5)(ii)).

If this proposed order is finalized, oncology therapeutic ISH-based test systems will be reclassified into class II (general controls and special controls) and will be subject to premarket notification requirements under section 510(k) of the FD&C Act. As discussed in this proposed order, the intent is for the reclassification to be codified in the new classification regulation 21 CFR 864.1890. Firms will be required to comply with the particular mitigation measures set forth in the special controls in their premarket notification submissions and upon clearance of their devices. Adherence to the special controls, in addition to the general controls, is necessary to provide a reasonable assurance of safety and effectiveness of oncology therapeutic ISH-based test systems.

VIII. Analysis of Environmental Impact

We have determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Paperwork Reduction Act of 1995

While this proposed order contains no new collections of information, it does refer to previously approved FDA collections of information. The previously approved collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501–3521). The collections of information in 21 CFR part 820 (Quality System Regulation) have been approved under OMB control number 0910–0073; the collections of information in part 807, subpart E (Premarket Notification Procedures), have been approved under OMB control number 0910–0120; and the collections of information in 21 CFR parts 801 and 809 (Device Labeling) have been approved under OMB control number 0910–0485.

X. Proposed Effective Date

FDA proposes that any final order based on this proposed order become effective 30 days after the date of its publication in the **Federal Register**.

XI. Codification of Orders

Under section 513(f)(3) of the FD&C Act, FDA may issue final orders to reclassify devices. FDA will continue to codify classifications and reclassifications in the Code of Federal Regulations (CFR). Changes resulting from final orders will appear in the CFR as newly codified orders. Therefore, under section 513(f)(3) of the FD&C Act, in the proposed order, we are proposing to codify In Situ Hybridization Test Systems for Use with a Corresponding Approved Oncology Therapeutic Product in the new 21 CFR 864.1890, under which these oncology therapeutic ISH-based test systems would be reclassified from class III into class II.

XII. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at *https://www.regulations.gov.* References without asterisks are not on public display at *https://www.regulations.gov* because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. Although FDA verified the website addresses in this document, please note that websites are subject to change over time.

* 1. In Vitro Companion Diagnostic Devices—Guidance for Industry and Food and Drug Administration Staff, issued August

6, 2014 (available at *https://www.fda.gov/media/81309/download*).
* 2. P980024/S001 Summary of Safety and Effectiveness, available at: *https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P980024*.
* 3. ''Guidance for Industry and for FDA Reviewers: Guidance on Section 216 of the Food and Drug Administration Modernization Act of 1997,'' issued on August 9, 2000 (available at *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-section-216-food-and-drug-administration-modernization-act-1997-guidance-industry-and-fda)*.
* 4. P040005 Summary of Safety and Effectiveness, available at: *https://www.accessdata.fda.gov/cdrh_docs/pdf4/P040005B.pdf*.
* 5. P050040 Summary of Safety and Effectiveness, available at: *https://www.accessdata.fda.gov/cdrh_docs/pdf5/P050040B.pdf*.
* 6. P100024 Summary of Safety and Effectiveness, available at: *https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100024B.pdf*.
* 7. P100027 Summary of Safety and Effectiveness, available at: *https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100027B.pdf*.
* 8. P110012 Summary of Safety and Effectiveness, available at: *https://www.accessdata.fda.gov/cdrh_docs/pdf11/P110012B.pdf*.
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List of Subjects in 21 CFR Part 864

Blood, Medical devices, Packaging and containers.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 864 be amended as follows:

PART 864—HEMATOLOGY AND PATHOLOGY DEVICES

■ 1. The authority citation for part 864 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360*l,* 371.

■ 2. Add § 864.1890 to subpart B to read as follows:

§ 864.1890 In situ hybridization test systems for use with a corresponding approved oncology therapeutic product.

(a) *Identification.* In situ hybridization (ISH) test systems indicated for use with a corresponding approved oncology therapeutic product are identified as prescription in vitro diagnostic devices consisting of nucleic acid probes intended for the qualitative or quantitative detection of specific nucleic acid sequences in human clinical specimens to provide information related to the use of a corresponding approved oncology therapeutic product as described in the corresponding approved oncology therapeutic product labeling.

(b) *Classification.* Class II (special controls). The special controls for this device are:

(1) Design verification and validation must include:

(i) Specification for risk mitigation elements intended to mitigate risks associated with testing and results interpretation, including controls, procedures, and user training requirements, as appropriate.

(ii) Specification of the criteria for test result interpretation and reporting, including device cut-off(s) (*i.e.,* clinical threshold(s) or the medical decision point(s) between positive and negative results) or other relevant criteria that distinguishes positive and negative or quantitative results. This information must include the rationale for the chosen cut-off(s) to include the upper reference of normal, or other relevant criteria and results supporting validation of the cut-off(s) evaluating borderline samples around the clinical threshold(s). Scoring criteria for all applicable signals must be provided.

(iii) Device performance data demonstrating appropriate analytical sensitivity provided from studies using interphase nuclei from intended use specimen type(s) that are considered karyotypically normal, or through an alternative approach, as determined to be appropriate by FDA (*e.g.,* probe sensitivity and probe limits).

(iv) Device performance data demonstrating appropriate analytical specificity of the device for the intended use specimen type(s), as determined to be appropriate by FDA (*e.g.,* probe specificity, interference study, cross-reactivity and cross contamination testing).

(v) Device performance data demonstrating appropriate precision and reproducibility of the device using clinical specimens representing the intended use specimen type(s) and intended use biomarker(s) from the intended use population and investigating major sources of variability (*e.g.,* multiple reagent lots, operators, instruments over multiple days, and inter- and intra-reader precision). If the device will be used at more than one site, data must demonstrate adequate reproducibility across multiple intended use sites. Additionally, precision and reproducibility of the device must be evaluated with specimens near the clinical decision threshold(s) and near the limits of reportable range. Additionally, device performance data demonstrating appropriate precision must be provided from studies evaluating the different signals and associated cut-offs and controls, as determined to be appropriate by FDA. Furthermore, precision of the device must be evaluated per specimen and in aggregate.

(vi) Device performance data demonstrating appropriate device robustness, as determined to be appropriate by FDA. The study must assess the tolerance ranges for various critical test and specimen parameters, as applicable.

(vii) Device performance data demonstrating linearity of quantitative results using samples covering the device measuring range, as applicable.

(viii) Device performance data demonstrating appropriate reagent stability for real-time and in-use stability; post-hybridization signal stability; and photostability of probe, as applicable.

(ix) Device performance data demonstrating appropriate specimen stability based on the intended use specimen type(s) of the device, as applicable.

(x) Clinical data generated using well-characterized clinical specimens representative of the intended use population demonstrating appropriate clinical performance of the device for its intended use, as determined to be appropriate by FDA.

(2) Labeling must include:

(i) An appropriate summary, as determined by FDA, of the performance studies performed and the results of

those studies, including those that relate to all design verification and validation special controls.

(ii) A limiting statement, as appropriate, that explains that the test results are intended to be interpreted by a qualified or appropriately trained reader in conjunction with other diagnostic laboratory test results and/or pathology test results, relevant clinical information, and proper controls.

(iii) Language indicating that the test system is indicated for use with a corresponding FDA-approved oncology therapeutic product and device labeling must be consistent with the information set forth in the corresponding FDA-approved oncology therapeutic product labeling.

Dated: June 5, 2025.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

[FR Doc. 2025–10549 Filed 6–10–25; 8:45 am]

BILLING CODE 4164–01–P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[EPA–R03–OAR–2024–0513; FRL–12075–01–R3]

Approval and Promulgation of Air Quality Implementation Plans; West Virginia; Revisions to Regulation for Control of Ozone Season Nitrogen Oxide Emissions

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: The Environmental Protection Agency (EPA) is proposing to approve a state implementation plan (SIP) revision submitted by the State of West Virginia. The revision pertains to West Virginia 45 Code of State Rules (CSR) 40 (WV rule) that establishes the nitrogen oxides (NO_X) ozone season limitations and requirements for non-electrical generating unit (EGU) large industrial boilers and combustion turbines that have a maximum design heat input of greater than 250 million British thermal units per hour (MMBtu/hr), as well as affected stationary internal combustion engines and cement manufacturing kilns. This action is being taken under the Clean Air Act (CAA).

DATES: Written comments must be received on or before July 11, 2025.

ADDRESSES: Submit your comments, identified by Docket ID No. EPA–R03–OAR–2024–0513 at *www.regulations.gov,* or via email to *gordon.mike@epa.gov.* For comments submitted at *Regulations.gov,* follow the online instructions for submitting comments. Once submitted, comments cannot be edited or removed from *Regulations.gov.* For either manner of submission, the EPA may publish any comment received to its public docket. Do not submit electronically any information you consider to be confidential business information (CBI) or other information whose disclosure is restricted by statute. Multimedia submissions (audio, video, etc.) must be accompanied by a written comment. The written comment is considered the official comment and should include discussion of all points you wish to make. The EPA will generally not consider comments or comment contents located outside of the primary submission (*i.e.,* on the web, cloud, or other file sharing system). For additional submission methods, please contact the person identified in the **FOR FURTHER INFORMATION CONTACT** section. For the full EPA public comment policy, information about CBI or multimedia submissions, and general guidance on making effective comments, please visit *https://www.epa.gov/dockets/commenting-epa-dockets.*

FOR FURTHER INFORMATION CONTACT: Michael Gordon, Planning & Implementation Branch (3AD30), Air & Radiation Division, U.S. Environmental Protection Agency, Region III, 1600 John F. Kennedy Boulevard, Philadelphia, Pennsylvania 19103. The telephone number is (215) 814–2039. Mr. Gordon can also be reached via electronic mail at *gordon.mike@epa.gov.*

SUPPLEMENTARY INFORMATION: On April 17, 2024, the State of West Virginia, through the West Virginia Department of Environmental Protection (WVDEP), submitted a revised version of West Virginia Legislative Rule 45CSR40-Control of Ozone Season Nitrogen Oxides Emissions (WV rule) for inclusion in the West Virginia SIP. This included two state revisions dated June 1, 2020 and April 1, 2023. The submission was supplemented on October 8, 2024, with additional information related to public noticing of the June 1, 2020 revision. The revisions to the WV rule included: (1) updating the characterization of units not subject to the rule because they are subject to a Federal NO_X ozone season trading program, and (2) amending monitoring requirements consistent with the Federal rule, ''Emissions Monitoring Provisions in State Implementation Plans Required Under the NO_X SIP Call'' (84 FR 8422, March 8, 2019).

I. Background

On October 27, 1998 (63 FR 57356), the EPA finalized the ''Finding of Significant Contribution and Rulemaking for Certain States in the Ozone Transport Assessment Group Region for Purposes of Reducing Regional Transport of Ozone'' (NO_X SIP Call). The NO_X SIP Call was designed to mitigate significant transport of NO_X, one of the precursors of ozone. The EPA developed the NO_X Budget Trading Program, an allowance trading program that states could adopt to meet their obligations under the NO_X SIP Call. The NO_X Budget Trading Program allowed EGUs greater than 25 megawatts and industrial non-electrical generating units, such as boilers and turbines, with a rated heat input greater than 250 MMBtu/hr, referred to as ''large non-EGUs'', to participate in a regional NO_X cap and trade program. The NO_X SIP call also established NO_X reduction requirements for other non-EGUs, including cement kilns and stationary internal combustion engines. The EPA has implementing regulations for the NO_X SIP Call at 40 CFR 51.121.

On May 12, 2005 (70 FR 25162), the EPA promulgated the Clean Air Interstate Rule (CAIR) to address transported emissions that significantly contributed to downwind states' nonattainment and maintenance of the 1997 ozone and fine particulate matter ($PM_{2.5}$) national ambient air quality standards (NAAQS). CAIR required 28 states, including West Virginia, to reduce emissions of NO_X and sulfur dioxide (SO_2), which are precursors to ozone and $PM_{2.5}$. Under CAIR, the EPA established separate cap and trade programs for annual ozone season and annual emissions.[1] On April 28, 2006 (71 FR 25328), the EPA also promulgated Federal Implementation Plans (FIP) requiring the EGUs in each affected state, but not large non-EGUs, to participate in the CAIR trading programs. States could comply with the requirements of CAIR by either remaining on the FIP, which applied only to EGUs, or by submitting a CAIR SIP revision that included as trading sources EGUs and the non-EGUs that formerly traded in the NO_X Budget Trading Program under the NO_X SIP Call. The EPA discontinued administration of the NO_X Budget

[1] CAIR developed three separate cap and trade programs that could be used to achieve the required reductions: the CAIR NO_X ozone season trading program, the CAIR annual NO_X trading program, and the CAIR annual SO_2 trading program. The CAIR NO_X ozone season and annual programs began in 2009, while the CAIR SO_2 annual program began in 2010.