December 21, 2018

Cytocell, Ltd
Xavier Baker
Regulatory Affairs Specialist
3-4 Technopark, Newmarket Road
Cambridge, CB5 8PB, UK

Re: DEN170070

Trade/Device Name:

MLL (KMT2A) Breakapart FISH Probe Kit
P53 (TP53) Deletion FISH Probe Kit
Del(20q) Deletion FISH Probe Kit
CBFβ (CBFB) /MYH11 Translocation, Dual Fusion FISH Probe Kit
Del(5q) Deletion FISH Probe Kit
Del(7q) Deletion FISH Probe Kit
AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion FISH Probe Kit
EVI1 (MECOM) Breakapart FISH Probe Kit

Regulation Number: 21 CFR 864.1880
Regulation Name: Fluorescent in-situ hybridization based detection of chromosomal abnormalities from patients with hematologic malignancies
Regulatory Class: Class II
Product Code: QDI
Dated: September 28, 2017
Received: September 29, 2017

Dear Xavier Baker:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your De Novo request for classification of the

MLL (KMT2A) Breakapart FISH Probe Kit,
P53 (TP53) Deletion FISH Probe Kit,
Del(20q) Deletion FISH Probe Kit,
CBFβ (CBFB) /MYH11 Translocation, Dual Fusion FISH Probe Kit,
Del(5q) Deletion FISH Probe Kit,
Del(7q) Deletion FISH Probe Kit,
AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion FISH Probe Kit, and
EVI1 (MECOM) Breakapart FISH Probe Kit,

which are all prescription devices with the following respective indications for use:

The MLL (KMT2A) Breakapart FISH Probe Kit is a fluorescence in situ hybridization (FISH) Test used to detect rearrangement of the MLL (KMT2A) region on chromosome 11 at location 11q23.3 in fixed bone marrow specimens from patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). The test is indicated for characterization of patient specimens consistent with World Health Organization (WHO) guidelines for Classification of Tumours of Haematopoietic and Lymphoid Tissues (Revised 4th Edition) and in conjunction with other clinicopathological criteria. The assay results are intended to be interpreted by a qualified pathologist or cytogeneticist. The test is not intended for use as a stand-alone diagnostic, disease screening, or as a companion diagnostic.

The P53 (TP53) Deletion FISH Probe Kit is a fluorescence in situ hybridization (FISH) Test used to detect deletion of the P53 (TP53) region on chromosome 7 at location 17p13 in fixed bone marrow specimens from patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). The test is indicated for characterization of patient specimens consistent with World Health Organization (WHO) guidelines for Classification of Tumours of Haematopoietic and Lymphoid Tissues (Revised 4th Edition) and in conjunction with other clinicopathological criteria. The assay results are intended to be interpreted by a qualified pathologist or cytogeneticist. The test is not intended for use as a stand-alone diagnostic, disease screening, or as a companion diagnostic.

The Del(20q) Deletion FISH Probe Kit is a fluorescence in situ hybridization (FISH) Test used to detect deletion within the long arm of chromosome 20 at locations 20q12 and 20q13.1, in fixed bone marrow specimens from patients with myelodysplastic syndrome (MDS). The test is indicated for characterization of patient specimens consistent with World Health Organization (WHO) guidelines for Classification of Tumours of Haematopoietic and Lymphoid Tissues (Revised 4th Edition) and in conjunction with other clinicopathological criteria. The assay results are intended to be interpreted by a qualified pathologist or cytogeneticist. The test is not intended for use as a stand-alone diagnostic, disease screening, or as a companion diagnostic.

The CBFβ (CBFB)/MYH11 Translocation, Dual Fusion FISH Probe Kit is a fluorescence in situ hybridization (FISH) Test used to detect rearrangement of the chromosome 16 causing the *CBFβ-MYH11* (*CBFB-MYH11*) fusion in fixed bone marrow specimens from patients with acute myeloid leukemia (AML). The test is indicated for characterization of patient specimens consistent with World Health Organization (WHO) guidelines for Classification of Tumours of Haematopoietic and Lymphoid Tissues (Revised 4th Edition) and in conjunction with other clinicopathological criteria. The assay results are intended to be interpreted by a qualified pathologist or cytogeneticist. The test is not intended for use as a stand-alone diagnostic, disease screening, or as a companion diagnostic.

The Del(5q) Deletion FISH Probe Kit is a fluorescence in situ hybridization (FISH) Test used to detect deletions within the long arm of chromosome 5 at location 5q31.2 in fixed bone marrow specimens from patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). The test is indicated for characterization of patient specimens consistent with World Health Organization (WHO) guidelines for Classification of Tumours of Haematopoietic and Lymphoid Tissues (Revised 4th Edition) and in conjunction with other clinicopathological criteria. The assay results are intended to be interpreted by a qualified pathologist or cytogeneticist. The test is not intended for use as a stand-alone diagnostic, disease screening, or as a companion diagnostic.

The Del(7q) Deletion FISH Probe Kit is a fluorescence in situ hybridization (FISH) Test used to detect deletions within the long arm of chromosome 7 at locations 7q22 and 7q31.2 in fixed bone marrow specimens from patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). The test is indicated for characterization of patient specimens consistent with World Health Organization (WHO) guidelines for Classification of Tumours of Haematopoietic and Lymphoid Tissues (Revised 4th Edition) and in conjunction with other clinicopathological criteria. The assay results are intended to be interpreted by a qualified pathologist or cytogeneticist. The test is not intended for use as a stand-alone diagnostic, disease screening, or as a companion diagnostic.

The AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion FISH Probe Kit is a fluorescence in situ hybridization (FISH) Test used to detect rearrangement involving the *AML1* (*RUNX1*) region on chromosome 21 at location 21q22.1 and the *ETO* (*RUNX1T1*) region on chromosome 8 at location 8q21.3 in fixed bone marrow specimens from patients with acute myeloid leukemia (AML). The test is indicated for characterization of patient specimens consistent with World Health Organization (WHO) guidelines for Classification of Tumours of Haematopoietic and Lymphoid Tissues (Revised 4th Edition) and in conjunction with other clinicopathological criteria. The assay results are intended to be interpreted by a qualified pathologist or cytogeneticist. The test is not intended for use as a stand-alone diagnostic, disease screening, or as a companion diagnostic.

The EVI1 (MECOM) Breakapart FISH Probe Kit is a fluorescence in situ hybridization (FISH) Test used to detect rearrangement involving the *EVI1* (*MECOM*) region on chromosome 3 at location 3q26.2, in fixed bone marrow specimens from patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). The test is indicated for characterization of patient specimens consistent with World Health Organization (WHO) guidelines for Classification of Tumours of Haematopoietic and Lymphoid Tissues (Revised 4th Edition) and in conjunction with other clinicopathological criteria. The assay results are intended to be interpreted by a qualified pathologist or cytogeneticist. The test is not intended for use as a stand-alone diagnostic, disease screening, or as a companion diagnostic.

Although this letter refers to your products as devices, please be aware that some granted products may instead be combination products. If you have questions on whether your product is a combination product,

contact CDRHProductJurisdiction@fda.hhs.gov. FDA concludes that this device should be classified into Class II. This order, therefore, classifies the

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Del(5q) Deletion FISH Probe Kit,
Del(7q) Deletion FISH Probe Kit,
AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion FISH Probe Kit, and
EVI1 (MECOM) Breakapart FISH Probe Kit,

and substantially equivalent devices of this generic type, into Class II under the generic name Fluorescence in-situ hybridization based detection of chromosomal abnormalities from patients with hematologic malignancies.

FDA identifies this generic type of device as:

Fluorescence in-situ hybridization based detection of chromosomal abnormalities from patients with hematologic malignancies. A fluorescence in-situ hybridization based detection of chromosomal abnormalities from patients with hematologic malignancies is used to detect chromosomal abnormalities in human specimens from patients with hematologic malignancies. The test is indicated for the clinical management of patients consistent with internationally accepted guidelines (e.g., World Health Organization guidelines for Classification of Tumours of Haematopoietic and Lymphoid Tissues) and in conjunction with other clinical and clinicopathological criteria. The results are to be interpreted by a pathologist or equivalent professional.

Section 513(f)(2) of the Food, Drug and Cosmetic Act (the FD&C Act) was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012. This law provides two options for De Novo classification. First, any person who receives a "not substantially equivalent" (NSE) determination in response to a 510(k) for a device that has not been previously classified under the Act may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. On December 13, 2016, the 21st Century Cures Act removed a requirement that a De Novo request be submitted within 30 days of receiving an NSE determination. Alternatively, any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act without first submitting a 510(k). FDA shall, within 120 days of receiving such a request, classify the device. This classification shall be the initial classification of the device. Within 30 days after the issuance of an order classifying the device, FDA must publish a notice in the Federal Register announcing the classification.

On November 29, 2017, FDA received your De Novo requesting classification of the
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Del(20q) Deletion FISH Probe Kit,
CBFβ (CBFB) /MYH11 Translocation, Dual Fusion FISH Probe Kit,
Del(5q) Deletion FISH Probe Kit,
Del(7q) Deletion FISH Probe Kit,

AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion FISH Probe Kit,
EVI1 (MECOM) Breakapart FISH Probe Kit.

The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the

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Del(5q) Deletion FISH Probe Kit,
Del(7q) Deletion FISH Probe Kit,
AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion FISH Probe Kit,
EVI1 (MECOM) Breakapart FISH Probe Kit,

into class I or II, it is necessary that the proposed class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use. After review of the information submitted in the De Novo request, FDA has determined that, for the previously stated indications for use, the

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Del(5q) Deletion FISH Probe Kit,
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EVI1 (MECOM) Breakapart FISH Probe Kit,

can be classified in class II with the establishment of special controls for class II. FDA believes that class II (special) controls provide reasonable assurance of the safety and effectiveness of the device type. The identified risks and mitigation measures associated with the device type are summarized in the following table:

Table 1 – Identified Risks to Health and Identified Mitigations

Identified Risks to Health	Mitigation Measures
Incorrect test results	Special controls (1), (2), (3), and (4)
Incorrect interpretation of test results	Special controls (1), (2), (3), and (4)

In combination with the general controls of the FD&C Act, the Fluorescent in-situ hybridization based detection of chromosomal abnormalities from patients with hematologic malignancies is subject to the following special controls:

(1) Design verification and validation must include:

(i) A detailed description of all probes included in the kit;

(ii) Purpose of each probe;

(iii) Probe molecular specificity;

(iv) Probe specificity;

(v) Probe limits;

(vi) Probe sensitivity;

(vii) Specification of required ancillary reagents, instrumentation, and equipment;

(viii) Specification of the specimen collection, processing, storage and slide preparation methods;

(ix) Specification of the assay procedure;

(x) Specification of control elements that are incorporated into the recommended testing procedures;

(xi) Specification of the criteria for test result interpretation and reporting;

(xii) Documentation demonstrating analytical validation that includes:

(A) Device analytical sensitivity data with a minimum of 25 specimens from karyotypically normal males.

(B) Device analytical specificity data with a minimum of 5 specimens from karyotypically normal males.

(C) Description of how the clinical threshold was assigned and verification of the assigned clinical threshold.

(D) Device precision/reproducibility data with a minimum of 6 clinical specimens including 2 negative specimens, 2 positive specimens near the clinical decision threshold (cut-off) and 2 positive specimens. The data must include results obtained from 3 sites (as applicable), with 2 operators at each site, with the assay run for a minimum of 3-5 non-consecutive days and each specimen run in duplicate for a minimum of 30 replicates.

(E) Between-reagent lot reproducibility using 3 reagent lots and 3 clinical specimens representing negative, near cut-off /low positive, and positive.

(F) Device stability data to include:

(1) Real-time Stability,

(2) Freeze-Thaw Stability,

(3) Transport and Temperature Stability, as applicable,

(4) Post-Hybridization Signal Stability, and

(5) Photostability of Probe.

(xiii) Documentation demonstrating the clinical validity of the device that includes:

(A) A summary of the prevalence and clinical thresholds reported in 3 peer-reviewed published literature references for the intended use population of the device and device performance data demonstrating conformance with the published prevalence as reported in peer-reviewed published literature references based on testing clinical specimens, selected without bias (e.g., consecutively selected) from the intended use population using the specific device seeking marketing clearance. A minimum number of clinical specimens must be tested to ensure sufficient positives are evaluated by the device, or alternatively, in the absence of a sufficient number of positives, an additional comparison of results obtained with the device to clinical truth (e.g., confirmed clinical diagnosis and/or G-banded karyotyping) with an independent specimen set must be conducted.

(B) Documentation for peer–reviewed published literature references must include the following elements:

(1) Whether the specific device was used in the literature reference;

(2) Number and type of specimens;

(3) Target population studied;

(4) Upper reference limit; and

(5) Prevalence range estimated based on the number of positive probe results.

(C) In the absence of clinical data obtained from paragraphs (b)(1)(xiii)(A) and (b)(1)(xiii)(B) of this section, clinical data obtained from a method comparison to the predicate with positives and negative clinical specimens.

(2) The intended use required on the label under 21 CFR 809.10(a)(4) and on the labeling under 21 CFR 809.10(b)(5)(ii), must include a statement that

"The test is not intended for use as a stand-alone diagnostic, disease screening, or as a companion diagnostic."

(3) The 21 CFR 809.10(b) labeling must include information that demonstrates the performance characteristics of the test, including a detailed summary of the performance studies conducted and their results, as described in paragraphs (b)(1)(iv) through (b)(1)(xiii) of this section. The 21 CFR 809.10(b) labeling must include the pre-specified acceptance criteria for these

performance studies, justification for the pre-specified acceptance criteria, and whether the pre-specified acceptance criteria were met.

(4) The 21 CFR 809.10(b) labeling must include the following limiting statements:

(i) "Reporting and interpretation of FISH results should be consistent with professional standards of practice and should take into consideration other clinical and diagnostic information. This kit is intended as an adjunct to other diagnostic laboratory tests and therapeutic action should not be initiated on the basis of the FISH result alone. Failure to adhere to the protocol may affect the performance and lead to false results."

(ii) "Each lab is responsible for establishing their own cut-off values. Each laboratory should test sufficiently large number of samples to establish normal population distribution of the signal levels and to assign a cut-off value. The product is for professional use only and is intended to be interpreted by a qualified Pathologist or Cytogeneticist."

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 type. FDA has determined premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device type and, therefore, the device is not exempt from the premarket notification requirements of the FD&C Act. Thus, persons who intend to market this device type must submit a premarket notification containing information on the Fluorescent in-situ hybridization based detection of chromosomal abnormalities from patients with hematologic malignancies they intend to market prior to marketing the device.

Please be advised that FDA's decision to grant this De Novo request does not mean that FDA has made a determination that your device complies with other requirements of the FD&C Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the FD & C Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm597488.htm); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and if applicable, the electronic product radiation control provisions (Sections 531-542 of the FD & C Act); 21 CFR 1000-1050.

A notice announcing this classification order will be published in the Federal Register. A copy of this order and supporting documentation are on file in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852 and are available for inspection between 9 a.m. and 4 p.m., Monday through Friday.

As a result of this order, you may immediately market your devices as described in the De Novo request, subject to the general control provisions of the FD&C Act and the special controls identified in this order.

For comprehensive regulatory information about medical devices and radiation-emitting products, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

If you have any questions concerning the contents of the letter, please contact Bowen Cui at 240-402-6148.

Sincerely,

Donna M. Roscoe -S

For Reena Philip, Ph.D.
Director
Division of Molecular Genetics and Pathology
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health