

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION  
DECISION SUMMARY  
INSTRUMENT ONLY TEMPLATE**

**A. 510(k) Number:**

K061602

**B. Purpose for Submission:**

Addition to the BioView Duet System of fluorescence in situ hybridization enumeration of the HER-2/neu gene for human breast cancer specimens

**C. Manufacturer and Instrument Name:**

BioView Ltd.

Duet™ System

**D. Type of Test or Tests Performed:**

Automated fluorescence in situ hybridization (FISH) enumeration of the HER-2/neu gene in human breast cancer specimens

**E. System Descriptions:**

1. Device Description:

The Duet system is an automated scanning microscope and image analysis system. The Duet System workstation integrates a microscope, CCD camera, motorized stage, computer, keyboard, mouse, joystick, monitor and a dedicated software program. The Duet System scans cell samples in high resolution and in full color at high speed both in bright light and fluorescent illumination. The Duet System suggests classification of the cells according to their morphological features, their staining and fluorescent signals and allows the user to quickly examine the results, correct them as needed and generate a report summarizing the sample's data. The unique feature of the Duet System allows the combined presentation of morphological and specific staining information of the same cell, for all the cells of the sample.

This particular application of the Duet system involves detection and quantification of chromosome 17 and the HER-2/neu gene via fluorescence in situ hybridization (FISH) in interphase nuclei from formalin-fixed, paraffin embedded human breast cancer tissue specimens probed by the Vysis® PathVysion™ HER-2 DNA Probe kit.

2. Principles of Operation:

Samples are prepared according the instructions for the Vysis® PathVysion™ HER-2 DNA Probe kit. The user selects the appropriate areas for analysis in accordance with the PathVysion™ kit instructions. The Duet System automatically captures images for each of the selected areas and the automatic algorithm detects and enumerates the fluorescent signals. The user reviews the signal enumeration for all relevant cells and the results (total number of cells and overall signal ratio) are automatically calculated by the system.

There is no change in the system hardware from the previously cleared system. Software changes were implement to support the new indication for use for HER-2/neu FISH automated enumeration. The device methodology is well established.

3. Modes of Operation:

Semi-automated computer assisted interpretation

4. Specimen Identification:

Rack/positioning

5. Specimen Sampling and Handling:

Specimens are formalin-fixed, paraffin embedded human breast cancer tissue specimens probed for via fluorescence in situ hybridization (FISH) in interphase nuclei by the Vysis® PathVysion™ HER-2 DNA Probe kit

6. Calibration:

The system requires periodic calibration which should be performed only by BioView authorized personnel.

7. Quality Control:

Control slides are prepared and run concurrently with patient slides according to the PathVysion™ Kit instructions. The control slides are tested on the Duet™ System according to the same procedure as patient slides. It is the responsibility of the pathologist to assure the control slides meet quality acceptance criteria.

8. Software:

FDA has reviewed applicant's Hazard Analysis and Software Development processes for this line of product types:

Yes x or No \_\_\_\_\_

## **F. Regulatory Information:**

### 1. Regulation section:

21 CFR §864.5260 Automated cell-locating devices

21 CFR §866.4700 Automated fluorescence in situ hybridization (FISH) Enumeration Systems

### 2. Classification:

Class II

### 3. Product code:

JOY

NTH

### 4. Panel:

Hematology (81) and Immunology (82)

## **G. Intended Use:**

### 1. Indication(s) for Use:

The Duet™ System is an automated scanning microscope and image analysis system. It is intended for in vitro diagnostic use as an aiding tool to the pathologist in the detection, classification and counting of cells of interest based on color, intensity, size, pattern, and shape. The Duet™ System is intended to:

- Detect hematopoietic cells stained by Giemsa stain, immunohistochemistry or ISH (with bright field and fluorescent) prepared from cell suspension.
- Detect amniotic cells stained by FISH (using direct labeled DNA probes for chromosomes X, Y, 13, 18 and 21).
- Detect cells in urine specimens, stained by FISH (using the Vysis UroVysion™ Bladder Cancer Recurrence Kit for chromosomes 3, 7, 17 and 9p21 locus), from subjects with transitional cell carcinoma of the bladder.
- Identify/detect and quantify chromosome 17 and the HER-2/neu gene via fluorescence in situ hybridization (FISH) in interphase nuclei from formalin-fixed, paraffin embedded human breast cancer tissue specimens, probed by the Vysis®PathVision™ HER-2 DNA Probe Kit. The Duet™ is to be used as an adjunctive automated enumeration tool, in conjunction with manual visualization, to assist in determining HER-2/neu gene to chromosome 17 signal ratio.

2. Special Conditions for Use Statement(s):

For prescription use.

**H. Substantial Equivalence Information:**

1. Predicate Device Name(s) and 510(k) numbers:

BioView Duet™ System K030192, K040591, K050840

Vysis AutoVysion™ System K041875

Applied Imaging Ariol HER-2/neu FISH System K041875

2. Comparison with Predicate Device:

Similarities				
Item	Device	Predicate		
Specimen type	Formalin-fixed paraffin-embedded human breast cancer tissue	BioView Duet	Vysis AutoVysion	Applied Imaging Ariol
		N/A	Same	Same
Method of cell detection	Colorimetric pattern recognition by microscopic examination of prepared cells by size, shape, and intensity of counter-stained nuclei as observed by an automated computer controlled microscopic and/or visual observation by a health care professional.	Same	Same	Same
Detection Method	Fluorescence in situ hybridization (FISH)	Same	Same	Same
Intended use	Intended for <i>in vitro</i> diagnostic use as an aiding tool to the pathologist in the detection, classification and	Same		Same

Similarities				
Item	Device	Predicate		
	counting of cells of interest based on color, intensity, size, pattern and shape			
Probe kit	Vysis PathVysion® HER-2 DNA Probe Kit	N/A	Same	Same
Device components	<ul style="list-style-type: none"> <li>• PC workstation</li> <li>• Camera</li> <li>• Monitor</li> <li>• Microscope</li> <li>• Motorized Stage</li> <li>• Software</li> </ul>	Same	Same	Same

Differences				
Item	Device	Predicate		
Filters	DAPI/FITC/TRITC Green, Red, Yellow	BioView Duet	Vysis AutoVysion	Applied Imaging Ariol
		Same	DAPI, Spectrum Green™ (SG) and Spectrum Orange™ (SO)	DAPI, Spectrum Green™ (SG) and Spectrum Orange™ (SO)
Microscope objectives	10x, 20x, 40x, 63x	Same	10x, 40x	1.25x, 5x, 10x, 20x, 40x

#### **I. Special Control/Guidance Document Referenced (if applicable):**

FDA Guidance for Industry and FDA Staff – Class II Special Controls Guidance Document: Automated Fluorescence in situ Hybridization (FISH) Enumeration Systems.

General Principles of Software Validation; Final Guidance for Industry and FDA Staff

## J. Performance Characteristics:

### 1. Analytical Performance:

#### a. *Accuracy:*

N/A

#### b. *Precision/Reproducibility:*

Five slides, which represent the range of the intended use were included in this study: two slides of the Vysis™ PathVysion™ negative control (target ratio 1.0), two slides of Vysis™ PathVysion™ mid-low amplified control (target ratio 1.8) near the medical decision point, and one highly amplified slide (target ratio > 2.3).

Within Run: Each slide was analyzed three times on the same system within the same day.

Day-to-Day: Each slide was analyzed three times on different days.

Site-to-Site: Each slide was analyzed three times at different sites (different operator, different system, and different day)

### Repeatability and Reproducibility for 3 FOVs

	Slide ID	Mean	Standard Deviation	Coefficient of Variation (%)
<b>“Within Run” Repeatability</b>	BV-1	1.72	0.10	5.61
	BV-2	1.75	0.05	3.02
	BV-3	1.04	0.02	2.21
	BV-4	1.04	0.10	9.70
	BV-5	6.25	0.81	12.90
<b>“Site to site” Reproducibility</b>	BV-1	1.73	0.06	3.53
	BV-2	1.81	0.17	9.27
	BV-3	0.98	0.05	4.59
	BV-4	1.06	0.08	7.12
	BV-5	6.66	2.12	31.92
<b>“Day to day” Reproducibility</b>	BV-1	1.77	0.08	4.41
	BV-2	1.78	0.06	3.25
	BV-3	1.02	0.01	0.56
	BV-4	1.04	0.06	5.35
	BV-5	6.03	0.70	11.70

c. *Linearity:*

N/A

d. *Carryover:*

N/A

e. *Interfering Substances:*

N/A

2. Other Supportive Instrument Performance Data Not Covered Above:

a. *Method Comparison with Manual Method:*

The substantial equivalence studies were based on comparison to conventional manual microscopy performed in accordance with the Vysis PathVysion® HER-2/neu DNA Probe kit.

The comparison study was conducted at four clinical sites. The study included a total of 70 cases, consisting of 33 cases of normal (ratios < 1.5), 21 cases in the “borderline” range (ratios between 1.5 and 2.5) and 16 cases of high amplification (ratios >2.5). Ratios  $\geq 2.0$  were interpreted as “FISH positive” or amplification present. Ratios < 2.0 were interpreted as “FISH negative” or no amplification.

For the manual method, the sites counted 20 cells and then calculated the average HER-2/chromosome 17 ratios. If the result was between 1.8 and 2.2, another 20 cells were counted (as per the reagent package insert recommendation) and the final ratio was based on the average from counting 40 cells. The same protocol was followed for the Duet method (automated). If the Duet reported a ratio between 1.8 and 2.2 with the first 20 cells, the operator was instructed to count another 20 cells and then the final average calculation from the 40 cells was reported.

**Summary of pooled results for 3 FOV**

		Manual scoring		
		-	+	Total
With Duet Method	Amplification			
	-	48	1	49
	+	0	21	21
Total		48	22	70

Total agreement was found to be 99% (69/70) with 95% CI (92%, 100%). Negative percent agreement is 100% (48/48), 95% CI (93%, 100%) and positive percent agreement 96% (21/22), 95% CI (77%, 100%). The overall agreement as measured by Kappa was 99%, 95% CI (90%, 100%).

*b. Optimal Number of Fields of View:*

Method comparison studies and reproducibility and repeatability studies above were conducted using both 3 and 6 FOVs to evaluate the optimal performance of the Duet System using a minimal number of FOVs. The correlation between results obtained from the Duet System 3 and 6 FOV analyses revealed a correlation of .996, with R-square = .993. In addition, the constant was near 0 (0.0084) and non-significant ( $t = 0.207$ ,  $p = 0.836$ ). Therefore, 3 FOV provides results that are sufficient for the effective performance of the Duet System.

**K. Proposed Labeling:**

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

**L. Conclusion:**

1. The submitted information in this premarket notification is complete and supports a substantial equivalence decision.