510(K) SUMMARY

510(K) Number K061602

5.1 Applicant's Name:

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5.3 Date Prepared:

June 2006

5.4 Trade Name:

Duet™ System

5.5 Classification Name:

- Automated cell-location device and:
- Automated Fluorescence *in situ* Hybridization (FISH) Enumeration Systems

5.6 Medical Specialty:

Hematology and Immunology

5.7 Product Code:

- Automated cell-locating devices, product code: JOY
- Automated Fluorescence in situ Hybridization (FISH) Enumeration Systems, product code: NTH

5.8 Device Class:

II

5.9 Regulation Number:

- Automated cell-locating devices (product code JOY, Regulation No. 864.5260)
- Automated Fluorescence in situ Hybridization (FISH) Enumeration Systems (product code NTH, Regulation No. 866.4700)

5.10 Panel:

Hematology and Immunology

5.11 Predicate Devices:

BioView Ltd. is relying on the combination of the following predicate devices and a standard procedure for the current Duet™ System substantial equivalence discussion:

- Duet™ System, manufactured by BioView Ltd., cleared under K030192, K040591 and K050840 (Product codes JOY and NTH)
- Ariol® HER-2/*neu* FISH, manufactured by Applied Imaging Corp., cleared under K043519 (product code NTH)
- Vysis® AutoVysion™ System, manufactured by Vysis Inc., cleared under K041875 (product code NTH)
- Human manual visualization of human breast cancer tissue specimens, probed by Vysis® PathVysion™ HER-2 DNA Probe Kit (Hereinafter, the Manual Method).

5.12 Performance Standards and Guidance:

No performance standards have been established for such device under Section 514 of the Federal Food, Drug, and Cosmetic Act. However, the Duet™ System complies with the following voluntary standards and Guidance:

- EN 61010-1
- EN 61326-1
- IEC 60601-1-4
- ISO 14971-1
- FDA Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Automated Fluorescence in situ Hybridization (FISH) Enumeration Systems (March 2005).
- General Principles of Software Validation; Final Guidance for Industry and FDA Staff, FDA, CDRH (January 2002).

5.13 Intended Use / Indication 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.
- 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® PathVysion™ 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.

5.14 Device Description:

The Duet™ System is a fully integrated imaging and scanning platform that automates time-consuming and difficult laboratory tasks of slide screening by making a significant reduction in time and labor currently required.

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 in high resolution and in full color cell samples at high speed both in bright light illumination and in fluorescent illumination.

The Duet™ System suggests classification of the cells according to their morphological features, their staining (Giemsa, IHC) 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.

5.15 Substantial Equivalence:

Intended Use

The intended use of the Duet™ System is expanded to include the detection and quantification of chromosome 17 and the HER-2/*neu* gene via fluorescence *in situ* hybridization (FISH) in human breast cancer tissue specimens, probed by the Vysis® PathVysion™ HER-2 DNA Probe Kit (the PathVysion™ 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. Besides the additional indication, the Intended Use and Indication for Use statement of the Duet™ System were not changed.

Detection, classification and counting of HER-2/*neu* gene amplification via fluorescence *in situ* hybridization (FISH) in human breast cancer tissue specimens, probed by the PathVysion™ Kit, are routinely performed manually at the specialized laboratories using conventional microscopes, according to the instructions provided with the approved kit. The claim of an automated aiding tool for the detection and enumeration of FISH signals is also claimed by the 510(k)-cleared automatic enumeration predicate devices, the Vysis® AutoVysion™ System, the Ariol® HER-2/*neu* FISH and the previously cleared Duet™ System. Both the Vysis AutoVysion™ System and the Ariol® HER-2/*neu* FISH, similar to the Duet™ System, are intended for *in vitro* diagnostic use as an aid to the pathologist in the detection, classification, and counting of cells of interest based on particular color, intensity, size, pattern, and shape. In particular, the specific indication of HER-2/*neu* gene amplification detection via fluorescence *in situ* hybridization (FISH) in formalin-fixed, paraffin-embedded human breast cancer tissue specimens, probed by the PathVysion™ Kit, is common to the Duet™ System and to both these predicates.

The new intended use was supported by a comparative performance study demonstrating that the operation of the Duet™ System is safe and effective for this application in comparison to manual microscopy. This study, which is summarized below, further confirms that any minor differences between the manual and the automated Duet™ System do not raise any issue of safety or efficacy.

Technological Characteristics and Mode of Operation

The current Duet™ System is the same system as the 510(k)-cleared Duet™ System. No change was required to be incorporated to the system's hardware to support the new indication, and only minor software changes, including new algorithm for the automatic calculation of the overall amplification ratio of HER-2/*neu* gene, were made. All these changes were fully verified and validated through software verification and validation. The performance study described below

further confirms that any minor differences between the manual and the automated Duet™ System do not raise any issue of safety or efficacy.

5.16 Performance Characteristics of the Duet™ System:

A performance evaluation study was performed in order to evaluate the performance of the Duet™ System for the detection of amplification of the HER-2/*neu* gene via FISH in human breast cancer tissue specimens, probed by the PathVysion™ Kit, in terms of its accuracy in comparison to the manual system, and its reproducibility and repeatability.

The performance evaluation study report is comprised of the following four studies, which are summarized below:

Study 1 – Methods Comparison - a comparison of the Duet™ System method to manual scoring method.

Study 2 – Precision/Reproducibility Performance - an evaluation of the performance of the Duet™ System in terms of reproducibility and repeatability, within a system and across systems.

Study 3 – The Optimal Number of Fields of View - a determination of the optimal number of Fields of View required to be captured by the system for accurate sampling of the specimen.

Study 4 – Methods Comparison at the Borderline Range. A comparison of the Duet™ System method to manual scoring method at the borderline range.

5.16.1 Methods Comparison with Predicate Device

The purpose of this study was to demonstrate the accuracy of the Duet™ System method for detection of amplification of the HER-2/*neu* gene via fluorescence *in situ* hybridization (FISH) in human breast cancer tissue specimens, probed by the PathVysion™ Kit, in comparison to the manual scoring method.

The study was conducted in four (4) sites, which followed the same study protocol. A total of 56 specimen slides, prepared from human breast cancer tissue specimens in various stages of the disease, representing the entire intended use population, were probed by the PathVysion™ Kit according to the manufacturer instructions. Each slide was screened both manually and using the Duet™ system.

For the purpose of the agreement analysis between the manual and the Duet™ System, 'Amplification' scoring ("FISH positive") was defined as a ratio of $\geq$ 2.0 and 'No-Amplification' scoring (FISH negative") was

defined as a ratio of < 2.0, in accordance with the definition of the PathVysion™ Kit's package insert.

The statistical analysis performed for the pooled results included levels of agreement, positive predictive accuracy (PPA), negative predictive accuracy (NPA) and Kappa coefficient (along with associated 95% confidence intervals). High correlation was found between the manual method and the results of the Duet™ System method, showing excellent accuracy in detecting normal and abnormal samples, as defined by the PathVysion™ Kit, as summarizes in the table below:

	Proportion	95% Lower confidence limit	95% Upper confidence limit
NPA	100%	91%	100%
PPA	100%	82%	100%
Overall	100%	94%	100%
Kappa	100%	100%	100%

Analysis of Agreement between Methods and Predictive Values, Pooled Results. (PPA, Positive Predictive Accuracy; NPA, Negative Predictive Accuracy; Overall, Overall Percentage Agreement) – 3 FOVs Analysis

No significant differences between the studies in the four (4) sites were found rendering the pooled analysis valid.

In addition, the linear regression and bias estimation performed according to [NCCLS-EP9] further demonstrates the high level of agreement between the Duet™ System and the manual method throughout the entire range of the intended use population.

Further analysis of the pooled results of Study-1 (randomly selected samples, representing the entire intended-use population) and the additional samples of Study-4 (pre-selected to represent the borderline of 1.5-2.5), "Analysis of all Methods Comparison Studies Results" is presented in Section 15.16.4 below.

5.16.2 Precision/Reproducibility Performance

The purpose of this study was to evaluate the precision of the Duet™ System, for its performance with the PathVysion™ Kit, in terms of reproducibility and repeatability within a system and across systems and sites. For this purpose, the Duet™ System was evaluated using the following three (3) studies:

- Within Run: Each slide was analyzed three times in succession on the same system, within the same day
- Day-to-Day: Each slide was analyzed three times, each time on a different day

- Site-to-Site: Each slide was analyzed three times, each time in a different site

Five (5) slides, which represent the range of the intended use were included in this study: two (2) slides of the PathVysion™ Negative control (target ratio 1.0), two (2) slides of PathVysion™ Mid-low Amplified Control (target ratio 1.8, near the medical decision point), and one highly amplified slide (target ratio > 2.3). All slides were prepared according to the probe manufacturer's instructions.

The statistical analyses performed include estimating the average value, standard deviation and percent coefficient of variation (CV) for each slide separately for repeatability, lab reproducibility and day reproducibility.

Test results obtained for three (3) FOVs analysis demonstrated that CV values were usually low and ranged between 0.56 and 12.90 % for all cases. Only one exception was seen is laboratory reproducibility for one of the sample with a CV of 31.92%, resulted from very high amplification, which avoided accurate spot counting. Considering this objective problem of accuracy, good repeatability and reproducibility for the Duet™ System was demonstrated.

Therefore it can be concluded that the Duet™ System was proven to have high values of repeatability within run, between days and between sites, for three (3) FOVs analyses.

5.16.3 The Optimal Number of Fields of View

Method comparison studies and reproducibility and repeatability studies 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.

5.16.4 Methods Comparison at the Borderline Range

The purpose of this study was to further demonstrate the accuracy of the Duet™ System method for detection of amplification of the HER-2/*neu* gene via fluorescence *in situ* hybridization (FISH) in human breast cancer tissue specimens, probed by the PathVysion™ Kit, in comparison to the manual scoring method, in the borderline range.

For this purpose, a total of 21 human breast cancer tissue specimen slides, representing a borderline range [1.5-2.5], were selected,

including the seven (7) borderline samples of this range from Study-1 and additional new fourteen (14) borderline samples collected from additional site.
A combined analysis of these results with the results of the seven (7) borderline samples from Study-1 was performed. All slides used for the analysis were human clinical specimens prepared from breast cancer tissues, probed by the PathVysion™ Kit according to the manufacturer instructions and which were found to be in the predefined borderline range [1.5-2.5].

For the purpose of the analysis of the agreement between the manual and the Duet™ System, the same criteria used in Study-1 (Method Comparison) were used. Thus, 'Amplification' scoring ("FISH positive") was defined as a ratio of ≥ 2.0 and 'No-Amplification' scoring ("FISH negative") was defined as a ratio of < 2.0, as defined in the PathVysion Kit's package insert.
The statistical analysis performed, summarized in the table below, included levels of agreement, positive predictive accuracy (PPA), negative predictive accuracy (NPA) and Kappa coefficient (along with associated 95% confidence intervals) demonstrates high correlation between the manual method and the results of the Duet™ System method at the borderline range, showing excellent accuracy in detecting normal and abnormal samples.

	Proportion	95% Lower confidence limit	95% Upper confidence limit
NPA	100%	78%	100%
PPA	83%	36%	100%
Overall	95%	76%	100%
Kappa	88%	64%	100%

Analysis of Agreement between Methods and Kappa values, Borderline results. (PPA, Positive Predictive Accuracy; NPA, Negative Predictive Accuracy; Overall, Overall Percentage Agreement) – 3 FOVs Analysis

Analysis of the Results of Method Comparison Studies (Studies 1 and 4)

Statistical analysis of all method comparison studies, including all results from Study-1 (randomly selected samples, representing the entire intended-use population) as well as all the additional fourteen (14) samples of Study-4 (pre-selected to represent the borderline of 1.5-2.5) was performed. This analysis included levels of agreement, positive predictive accuracy (PPA), negative predictive accuracy (NPA) and Kappa coefficient (along with associated 95% confidence intervals).

As demonstrated in the table below, high correlation was found between the Manual Method and the results of the Duet™ Method in the pooled-method comparison studies analysis, showing excellent accuracy in detecting normal and abnormal samples, as defined by the manual Method.

	Proportion	95% Lower confidence limit	95% Upper confidence limit
NPA	100%	93%	100%
PPA	96%	77%	100%
Overall	99%	92%	100%
Kappa	97%	90%	100%

Analysis of Agreement between Methods and Kappa Values, Method Comparison Pooled-studies Results. (PPA, Positive Predictive Accuracy; NPA, Negative Predictive Accuracy; Overall, Overall Percentage Agreement) - 3 FOVs Analysis

Conclusions from the Performance Characteristics Study:
The comparison between the Duet™ System method and the Manual Microscopy Method demonstrated that the Duet™ system is effective and suitable for detection of amplification of the HER-2/*neu* gene via fluorescence *in situ* hybridization (FISH) in human breast cancer tissue specimens, probed by the Vysis™ PathVysion™ HER-2 DNA Probe Kit. The system performs adequately and produces reliable results allowing the trained lab technician operator to reliably assess the specimens with the accuracy needed for clinical use.

In addition to this performance evaluation, the comprehensive testing program, which was developed and performed in order to verify that the current Duet™ System does not raise any new safety and effectiveness issues in comparison to its predicate devices, included the following main parts:

- Software verification and validation testing, which was performed to evaluate the performance of the current version of the Duet™ System software and to verify that it performs according to its specifications.

- Risk analysis activities were performed in compliance with the requirements of ISO 14971-1 "Application of risk management to medical devices" (2000). As concluded from the Risk Analysis procedure, the potential risks of the Duet™ System have been reduced to the pre-determined acceptance criteria. Therefore, it was concluded that the risk level of the Duet™ System is acceptable.

5.17 Conclusion:

BioView Ltd. believes that the Duet™ System is substantially equivalent to the combination of its predicate devices in terms of Intended Use, Indications for Use, technological characteristics and mode of operation. Any minor differences between the Duet™ System and its predicate devices do not raise new safety or effectiveness issues, based on the performance results and the analysis of similarities and differences presented above.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

BIOVIEW LTD.
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7 Jabotinsky Street
Ramat Gan
Israel 52520

JAN 23 2007

Re: k061602
Trade/Device Name: Duet System
Regulation Number: 21 CFR 864.4700
Regulation Name: Automated Fluorescence *in situ* Hybridization (FISH) Enumeration System
Regulatory Class: Class II
Product Code: NTH, JOY
Dated: June 6, 2006
Received: June 8, 2006

Dear Ms. Winitz:
We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.
This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally

marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at (240) 276-0450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (240) 276-3150 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Robert L. Becker, Jr., MD, PhD
Director
Division of Immunology and Hematology
Office of In Vitro Diagnostic Device
Evaluation and Safety
Center for Devices and
Radiological Health

Enclosure

cc: HFZ-401 DMC

HFZ-404 510(k) Staff
HFZ- 440 Division
D.O.

K061602

Indications for Use

510(k) Number (if known): K061602

Device Name: Duet™ System

Indications 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.
- 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® PathVysion™ 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.

Prescription Use √ AND/OR Over-The-Counter Use _____
(Part 21 CFR 801 Subpart D) (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

Division Sign-Off

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Office of In Vitro Diagnostic Device
Evaluation and Safety

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