3/18/99

K983336

510(k) Summary
Safety and Effectiveness

This summary of safety and effectiveness information has been prepared in accordance with the requirements of SMDA 1990 and 21 CFR Part 807.92.

Name: **Address:**	Diagnostic Products Corporation 5700 West 96th St Los Angeles, CA 90045-5597
Telephone Number: **Facsimile Number:**	(310) 645-8200 (310) 645-9999
Contact Person:	Edward M. Levine, Ph.D. Director of Clinical Affairs
Date of Preparation:	March 16, 1999
Device Name:	
Trade:	PathoDx Respiratory Virus Panel
Catalog Number:	PKRP1
Common:	Direct immunofluorescence test for the qualitative detection of seven common respiratory viruses.
Classification:	Class II device, 83-GNW (21CFR866.3330)
Panel:	Microbiology
Manufacturer:	Diagnostic Products Corporation 5700 West 96th St Los Angeles, CA 90045
Establishment Registration #:	DPC's Establishment Registration Number is 2017183
Substantially Equivalent Predicate Device:	Bartels Viral Respiratory Screening and Identification Kit (K896635) Light Diagnostic Respiratory Viral Screen Indirect Immunofluorescence Assay by Chemicon International,Inc. (K922801)
Description of the Device:	Direct immunofluorescence test for the qualitative detection of seven common respiratory viruses.

Intended Use of the Device:

DPC's PathoDx Respiratory Virus Panel kit is a direct immunofluorescence test for the qualitative detection of seven common respiratory viruses (respiratory syncytial virus, influenza A, influenza B, parainfluenza viruses 1, 2, and 3, and adenovirus) in prepared direct patient specimens and following growth in cell culture. The materials supplied are intended for *in vitro diagnostic* use only.

Summary and Explanation of the Test:

Viral respiratory diseases in children and adults cause significant morbidity and mortality, especially in young children and older adults. About 75% of the acute respiratory illnesses are caused by viruses. With the availability of anti-viral therapy for some viruses, determination of a viral etiology for respiratory infections is important. Early and appropriate use of effective antiviral therapy can decrease morbidity and mortality associated with lower respiratory tract viral infections.

The laboratory diagnosis of viral infections is usually accomplished by serology, culture isolation/confirmation, and direct detection. The drawback to serological diagnosis is the delay and inconvenience of obtaining acute and convalescent phase sera. Culture isolation/confirmation is the standard method for most clinical virology laboratories. Although it is not as rapid as detection from direct patient specimens, culture isolation/confirmation is still the most sensitive method for detecting viral respiratory pathogens. Direct detection of viral antigen in patient specimens provides rapid diagnosis with possible anti-viral treatment. The direct method is invaluable in situations where virus lability may lead to low recovery rates by cell culture, as is the case for respiratory syncytial virus (RSV).

Respiratory specimens (nasopharyngeal aspirates or swabs) are tested for the presence of viral antigen. Direct viral antigen testing, combined with shell vial centrifugation-enhanced culture and conventional tube culture, provide rapid and accurate diagnosis of common viral etiologies of respiratory tract infections.

Respiratory Syncytial Virus (RSV)

Respiratory syncytial virus (RSV) is the major cause of acute viral respiratory disease in infants and young children. Illness occurs in about 10-40% of those children infected for the first time. It is responsible for 50% of all bronchiolitis cases and 25% of all pneumonia cases during the first months of life. RSV infection in older children and adults usually results in symptoms of a common cold, but it can also cause significant lower respiratory tract infection in adults, especially the elderly. RSV is distributed worldwide, causing annual winter outbreaks of respiratory disease, particularly in temperate climates. The virus is very contagious, and infected children shed virus for 1 to 2 weeks after they are admitted into the hospital and as long as 2 to 3 weeks overall. The high infectivity of RSV and the occurrence of re-infection despite the presence of circulating antibodies has made RSV the most frequent cause of nosocomial infection in

pediatric wards.

Ribavirin aerosol is used to treat RSV bronchiolitis and pneumonia. Early and rapid diagnosis of RSV infections is critical in order to initiate therapy and to control nosocomial infections. Immunofluorescence has been shown to be sensitive and specific for the detection of RSV antigens in nasopharyngeal secretions. These studies demonstrate that highly specific antibodies to RSV can be used for the detection of antigens in a direct patient specimen as well as in cell culture.

Cell culture isolation of RSV can be attained with a number of cell lines including HEp-2, HeLa, A549, and Vero cells. RSV cytopathic effect (CPE) may be visible as early as 2 days after innoculation, but some isolates can take up to 10 days.

Influenza Viruses

Influenza viruses are negative-stranded RNA viruses of the *Orthomyxoviridae* family. Influenza A and influenza B comprise a single genus, with influenza C in a separate genus.

Influenza A, and to a lesser extent influenza B, show antigenic variation in the hemagglutinin and neuraminidase proteins. Influenza A subtypes are identified by the hemagglutinin and neuraminidase antigens, H1-H13 and N1-N9, respectively. Minor changes in these antigens, called antigenic drift, occur yearly. Major changes due to reassortment of gene segments are called antigenic shift. These shifts can cause pandemics every 10 to 30 years. Strains H1N1, H3N2 have been associated with pandemics in humans.

Influenza infections are associated with seasonal outbreaks of respiratory disease such as pharyngitis, croup, bronchitis, and pneumonia. In the Northern hemisphere the "flu season" is from November to April, and from May to October in the Southern hemisphere. In tropical climates, influenza may be endemic with epidemics occurring more than once a year. Usually one type, either type A or B, will predominate during each epidemic.

Virus isolation and identification is the standard laboratory method for diagnosis. Tissue culture inoculation, rather than egg inoculation is the more usual method of isolation.

Spin-amplified shell vials used in combination with tissue culture can allow diagnosis within a day or so. Influenza A and B can be isolated in MRC-5, RD, A549, HL, and MDCK tube or shell vial cultures with or without the presence of trypsin. Influenza B usually produces CPE earlier than Influenza A, usually by 5-10 days post-infection. Hemagglutination or hemadsorption can be done before CPE is apparent with final viral identification confirmed by fluorescein-labeled monoclonal antibodies.

Parainfluenza Viruses

The parainfluenza viruses (PIV) belong to the genus *Paramyxovirus* which also includes RSV. Like the influenza viruses, the parainfluenza viruses also possess hemagglutinin, neuraminidase, and cell fusion activities. Four human parainfluenza virus serotypes have

been identified (types 1, 2, 3, and 4). Parainfluenza types 1, 2, and 3 are readily isolated by cell culture while parainfluenza type 4 is more difficult to cultivate.

The parainfluenza viruses and RSV compromise the most significant viral respiratory pathogens in infants and young children. The clinical diseases caused by parainfluenza viruses include rhinorrhea, cough, croup (laryngotracheobronchitis), bronchiolitis, and pneumonia. Types 1 and 2 are major causes of croup. Although type 3 infection can produce croup, type 3 is second only to RSV as the cause of bronchiolitis and pneumonia in infants less than 6 months of age. In older children and adults, parainfluenza virus infections may be asymptomatic or mimic the common cold. Type 4 has been associated only with mild upper respiratory tract infections in children and adults.

Cell culture isolation of parainfluenza viruses is usually done with primary rhesus monkey kidney cells or human kidney cell lines. Cell lines that have been successfully used for propagating parainfluenza viruses include RMK, HEK, LLC-MK2, Vero, A549, and HEp-2. Parainfluenza CPE, when present, is usually detectable 5-10 days post-inoculation. Presumptive confirmation of virus infection can be obtained by testing for hemadsoption of guinea pig erythrocytes with final identification of virus confirmed by fluorescein-labeled monoclonal antibodies.

Adenoviruses

Human adenoviruses are nonenveloped, double-stranded DNA viruses belonging to the family *Adenoviridae*. There have been 47 human serotypes identified with most serotypes associated with respiratory or ocular infections. Upper respiratory illness is mild. Lower respiratory disease caused by types 3, 4, 7, and 21 can result in bronchitis, croup, bronchiolitis, and pneumonia. Adenovirus infections in adults are not significant, with the exception of infections in immunocompromised hosts and occasional outbreaks in military recruit populations.

The PathoDx Respiratory Virus Panel kit can be used to provide rapid and accurate identification of viral respiratory pathogens by direct detection of prepared patients specimens or in confirmation or cell culture isolates.

Technology Comparison:

The **PathoDx Respiratory Virus Panel** kit consists of one screening reagent containing monoclonal antibodies to each respiratory virus and seven virus-specific monoclonal antibody reagents. All reagents contain monoclonal antibody labeled with fluorescein. Acetone-fixed cells from either patient specimens or cell culture are stained with the Screening Reagent and the Negative Control Reagent. The Screening Reagent contains fluorescein-labeled monoclonal antibodies to RSV, influenza A, influenza B, parainfluenza viruses 1, 2, and 3, and adenovirus. They will react specifically to any of the above viral antigens, if present in the cell. The Negative Control Reagent contains fluorescein-labeled murine antibodies which do not react with the viral agents. Unbound antibody and Evans blue counterstain are washed off with buffered saline, and the slide is mounted with buffered glycerol. Under fluorescence microscopy, the viral antigens recognized by the monoclonal antibodies present will show a characteristic apple-green

fluorescence, while uninfected cells will counterstain red with Evans blue. To identify which of the seven respiratory viruses is reactive with the Screening Reagent, acetone-fixed cell preparations are stained with each of the seven virus-specific reagents, washed free of unbound antibody, mounted with buffered glycerol, and observed under fluorescence microscopy. The responsible virus(es) will show characteristic apple-green fluorescence with uninfected cells counterstaining red.

Bartels Viral Respiratory Screening and Identification Kit utilizes an indirect fluorescent antibody staining technique for identifying virus in infected tissue culture and prepared patient specimens. The test consists of two immunological reagents. An anti-viral mouse monoclonal antibody which is unconjugated is applied to fixed cells and binds the viral antigen in question, if present in the cell substrate. Adenovirus and parainfluenza types 1, 2, and 3 reagents contain only a single monoclonal antibody; influenza A and B and RSV reagents contain two monoclonal antibodies in each reagent. A wash with phosphate buffered saline with pH 7.0 – 7.8 removes all unbound anti-viral antibody. Next, an anti-mouse immunoglobulin which is conjugated to fluorescein isothiocyanate (FITC) is added to the specimen. Again a wash is used to remove any unattached reagent, and the specimen is observed under a fluorescence microscope with the correct filter combination for FITC. Since several conjugated antiglobulins can attach to a single anti-viral antibody, an augmentation of fluorescence is achieved resulting in a highly sensitive staining technique. The use of monoclonal antibodies maximizes specificity. A positive reaction is one in which bright apple-green fluorescence is observed. Uninfected cells are counterstained with Evan's blue which is included in the conjugate, and appear dull red. As with all fluoresence assays, the quality of diagnosis depends on the sensitivity and specificity of reagents, capacity and condition of the fluorescence microscope, meticulous specimen collection and storage, and the skill of the laboratory worker in preparing patient specimens and interpreting the findings.

Light Diagnostics Respiratory Viral Screen (Distributed by Chemicon International, INC.) utilizes an indirect immunofluorescence technique for identifying virus in infected tissue cultures. The mouse monoclonal antibodies provided will bind to the appropriate viral antigen on the specimen slide. Unbound antibody is washed from the slide with Phosphate Buffered Saline (PBS). This is followed by the addition of FITC (fluorescein isothiocyanate) Labeled Goat Antibody is washed from the slide with PBS. FITC exhibits an apple green fluorescence when illuminated by ultraviolet light allowing visualization of the complex by microscopy. Cell fluorescence indicates a positive specimen. Non-infected cells stain a dull red due to the presence of Evans Blue in the FITC-labeled secondary antibody. The respiratory viral screen reagent is used to confirm the indiscriminate presence of respiratory viruses – adenovirus, respiratory syncytial virus, parainfluenza types 1, 2, & 3, and influenza A and B. The quality of the results will depend on a variety of factors such as the condition of the cell for culture confirmation, the fixative used, and the expertise of the technician performing the test.

Clinical Performance

The PathoDx Respiratory Virus Panel was evaluated in two clinical sites in the midwestern United States to determine the clinical performance of the panel and its individual constituents in detecting the presence of the seven respiratory viruses.

The first clinical site conducted two studies. The first study included 150 fresh specimens and 50 randomly selected retrospective samples. The specimens were from male and female patients with an age range from 8 days to 91 years. The specimens were primarily nasopharyngeal. The fresh specimens and the retrospective specimens (total n = 200) were screened by both direct smear and shell vial culture procedures using both PathoDx and Kit A respiratory virus assays. The specimens were also tested by the definitive cell culture procedure and individual virus tests by Kit A. The results for these tests are tabulated below. (One specimen was not tested in the direct smear procedure.)

	PathoDx Direct Smear			
Cell Culture	Positive	Negative	Sensitivity	Specificity
Positive	119	17	87.5%	100%
Negative	0	63		

Agreement: 91.5%
95% Confidence Limits for Sensitivity and Specificity, respectively: 80.7% - 92.5% and 94.3% - 100%.
Positive and Negative Predictive Values, respectively: 100% and 78.8%.

Of the 17 specimens negative in PathoDx direct smear but positive in cell culture, two were RSV positive; one was adenovirus positive; twelve were Influenza A positive and two were CPE with unidentified viruses.

The comparison between the PathoDx Respiratory Virus Panel direct smear test and Kit A's individual virus test showed 100% agreement for all specimens that were positive by Kit A's individual virus test.

Specimen Type	Positive by PathoDx Direct Smear	Positive by Kit A Individual	Agreement
RSV	18	18	100%
Influenza A	42	42	100%
Influenza B	12	12	100%
Parainfluenza 1	12	12	100%
Parainfluenza 2	11	11	100%
Parainfluenza 3	10	10	100%
Adenovirus	12	12	100%

Kit A Direct Smear	PathoDx Direct Smear Positive	Negative	Relative Sensitivity	Relative Specificity
Positive	119	0	100%	100%
Negative	0	80		

Agreement: 100%
95% Confidence Limits for Relative Sensitivity and Specificity, respectively: 96.9% - 100% and 95.5% - 100%.

The comparison between the PathoDx Respiratory Virus Panel shell vial culture test and Kit A's individual virus test showed that the PathoDx shell vial culture test detected all specimens that were positive by Kit A's individual virus test, with the exception of one RSV specimen.

Specimen Type	Positive by PathoDx Shall Vial	Positive by Kit A Individual	Agreement
RSV	17	18	94%
Influenza A	42	42	100%
Influenza B	12	12	100%
Parainfluenza 1	12	12	100%
Parainfluenza 2	11	11	100%
Parainfluenza 3	10	10	100%
Adenovirus	12	12	100%

Kit A Shell Vial	PathoDx Shell Vial Positive	Negative	Relative Sensitivity	Relative Specificity
Positive	129	0	100%	98.6%
Negative	1	70		

Agreement: 99.5%
95% Confidence Limits for Relative Sensitivity and Specificity, respectively: 97.2% - 100% and 92.4% - 100%.

The second study at this site included 168 retrospective, frozen cell culture isolates consisting of 29 specimens negative for all seven viruses and 139 specimens positive for one or more of the seven viruses. All specimens were screened by the cell culture procedures of both the PathoDx and Kit A respiratory virus assays.

Kit A Cell Culture	PathoDx Cell Culture Positive	Negative
Positive	138	1
Negative	0	29

Agreement: 99.4%

The positive specimens in the second study were confirmed positive by the cell culture individual virus procedures of both PathoDx and Kit A respiratory virus assays.

Specimen Type	Positive by PathoDx Cell Culture	Positive by Kit A Cell Culture	Agreement
RSV	30	30	100%
Influenza A	30	30	100%
Influenza B	21	21	100%
Parainfluenza 1	7	7	100%
Parainfluenza 2	13	14	93%
Parainfluenza 3	7	7	100%
Adenovirus	30	30	100%

The second clinical site, also in the midwestern United States, enrolled 185 randomly selected male and female patients who ranged in age from 1 day to 91 years. Fresh, mainly nasopharyngeal specimens were provided. One hundred and seventy-four specimens were tested by the direct smear procedure, and all 185 specimens were tested by the shell vial culture procedure using both PathoDx and Kit B Respiratory Viral Screen Indirect Immunofluorescence assay, with the following results.*

Kit B Direct Smear	PathoDx Direct Smear Positive	Negative
Positive	66	4
Negative	1	103

Agreement: 97.1%

Kit B Shell Vial	PathoDx Shell Vial Positive	Negative
Positive	43	2
Negative	4	136

Agreement: 96.8%

The difference in the number of positive specimens detected by the direct smear procedure and the shell vial procedure may be attributed to the prolonged transportation of specimens to this reference lab, thus reducing the viability of the virus.

*Unfortunately, contrary to the study protocol, cell cultures were not performed on all specimens, and only positive smears were stained.

Conclusion:

The data presented in this summary of safety and effectiveness is the data that the Food and Drug Administration used in granting DPC substantial equivalence for the PathoDx Respiratory Virus Panel.

Edward M. Levine

3/16/99

Edward M. Levine, Ph.D.
Director of Clinical Affairs

Date

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

MAR 18 1999

Edward M. Levine, Ph.D.
Director of Clinical Affairs
Diagnostic Products Corporation
5700 West 96th Street
Los Angeles, CA 90045-5597

Re: K983336
Trade Name: PathoDx® Respiratory Virus Panel
Regulatory Class: I
Product Code: LKT, GNY, GNX, GQS
Dated: January 6, 1999
Received: January 11, 1999

Dear Dr. Levine:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we 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). 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 (Premarket Approval), 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 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

Under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88), this device may require a CLIA complexity categorization. To determine if it does, you should contact the Centers for Disease Control and Prevention (CDC) at (770)488-7655.

This letter will allow you to begin marketing your device as described in your 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 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll free number (800) 638-2041 or at (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsmamain.html"

Sincerely yours,

Steven Gutman

Steven I. Gutman, M.D., M.B.A.
Director
Division of Clinical Laboratory Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

510(k) Number (if known):_____

Device Name: **PathoDx® Respiratory Virus Panel**

Indications For Use:

The PathoDx Respiratory Virus Panel (RVP) kit is a direct immunofluorescence test for the qualitative detection of 7 common respiratory viruses (respiratory syncytial virus, influenza A, influenza B, parainfluenza viruses 1,2, and 3, and adenovirus) in prepared direct patient specimens and following growth in cell culture. The materials supplied are intended for *in vitro* use only.

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

Woody Dickens

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K983336

Prescription Use X (Per 21 CFR 801.109) OR Over-The-Counter Use

(Optional Format 1-2-96)