DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date . MAY 20 1996

From Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

Subject Premarket Approval of Cytyc Corporation's ThinPrep® 2000 System - ACTION

To The Director, CDRH
ORA _____

ISSUE. Publication of a notice announcing approval of the subject PMA.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

(1) a premarket approval order for the above referenced medical device (Tab B); and

(2) the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.

Susan Alpert, Ph.D., M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

Approved _____ Disapproved _____ Date _____

Prepared by Louise E. Magruder, CDRH, HFZ-440, 5/13/96, 594-1293

1

P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food And Drug Administration

[DOCKET NO. _____]

Cytyc Corp.; PREMARKET APPROVAL OF ThinPrep® 2000 Processor

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by Cytyc Corp., Marlborough, MA, for premarket approval, under the Federal Food, Drug, and Cosmetic Act (the act), of the ThinPrep® 2000 System. After reviewing the recommendation of the Hematology and Pathology Devices Panel, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter of May 20, 1996, of the approval of the application.

DATES: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESSES: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Peter E. Maxim,

Center for Devices and Radiological Health (HFZ-440),

Food and Drug Administration,

2098 Gaither Rd.,

Rockville, MD 20850,

301-594-1293.

B

SUPPLEMENTARY INFORMATION: On November 22, 1995] Cytyc Corp., Marlborough, MA 01752, submitted to CDRH an application for premarket approval of the ThinPrep® 2000 System. The device is an automated cytology slide preparation instrument and is intended as a replacement for the conventional method of Pap smear preparation for use in screening for the presence of atypical cells, cervical cancer, or its precursor lesions (Low Grade Squamous Intraepithelial Lesions, High Grade Squamous Intraepithelial Lesions), as well as all other cytologic categories as defined by The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses.

On June 7, 1993, the Hematology and Pathology Devices Panel of the Medical Devices Advisory Committee, an FDA advisory committee, reviewed and recommended approval of the application. Cytyc Corp. withdrew the application and subsequently resubmitted the application on November 22, 1995.

On May 20, 1996,, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

Opportunity For Administrative Review

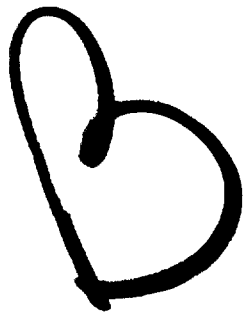
Section 515(d)(3) of the act,(21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act, for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under 21 CFR part 12 of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 21 CFR 10.33(b). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 515(d), 520(h) (21 U.S.C. 360e(d), 360j(h))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated:_____.

_____



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

Mr. Michael Adams, R.A.C.
Vice President,
Regulatory Affairs and Quality Assurance
Cytyc Corporation
237 Cedar Hill Street
Marlborough, Massachusetts 01752

MAY 20 1996

Re: P950039
ThinPrep® 2000 System
Filed: November 22, 1995
Amended: March 6, April 19, May 1, and May 7, 1996

Dear Mr. Adams:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the ThinPrep® 2000 System. This device is intended as a replacement for the conventional method of Pap smear preparation for use in screening for the presence of atypical cells, cervical cancer, or its precursor lesions (Low Grade Squamous Intraepithelial Lesions, High Grade Squamous Intraepithelial Lesions), as well as all other cytologic categories as defined by The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Peter E. Maxim, Ph.D., at (301) 594-1293.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

9

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

11

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984, and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices

(1) may have caused or contributed to a death or serious injury or

(2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for this PMA, you shall submit the appropriate reports required by the MDR Regulation and identified with the PMA reference number to the following office:

Division of Surveillance Systems (HFZ-531)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, 340
Rockville, Maryland 20850
Telephone (301) 594-2735

Events included in periodic reports to the PMA that have also been reported under the MDR Regulation must be so identified in the periodic report to the PMA to prevent duplicative entry into FDA information systems.

Copies of the MDR Regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. General Information

Device Generic Name: Cytology Slide Preparative Device

Device Trade Name: ThinPrep® Processor (TP 2000)

Applicant's Name and Address: Cytyc Corporation
237 Cedar Hill Street
Marlborough, Massachusetts

Premarket Approval Application (PMA) Number: P950039

Date of Panel Recommendation: June 7, 1993 (formerly P920009)

Date of Notice of Approval of Application: May 20, 1996

II. Indications for Use

A. Intended Use

The ThinPrep® 2000 System is intended as a replacement for the conventional method of Pap smear preparation for use in screening for the presence of atypical cells, cervical cancer, or its precursor lesions (Low Grade Squamous Intraepithelial Lesions, High Grade Squamous Intraepithelial Lesions), as well as all other cytologic categories as defined by The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses.

B. Patient Population

The intended patient population consists of all women who are screened for cervical neoplasia or its precursor lesions.

C. Background

The Papanicolaou (Pap) test was developed for early detection of cervical cancer and its precursors. Its effectiveness has been demonstrated through a reduction in the cervical cancer rate; however, it is not 100 percent effective in identifying all women with cancer or its precursor lesions (Koss, 1989).

III. Device Description

A. Device Components

The ThinPrep 2000 System consists of the following components:

ThinPrep 2000 Processor

PreservCyt Solution sample vial

TransCyt Filter Cylinder

ThinPrep Microscope Slides

B. Device Operation

The ThinPrep slide preparation process can be divided into three sample processing phases: dispersion, collection, and transfer.

1. Dispersion

The TransCyt Filter assembly rotates within the cell suspension, creating shear forces in the preservation solution that are strong enough to separate loosely joined material and disperse mucus, but have no adverse effect on the normal intracellular bonds found in sheets and clusters of exfoliated cells.

16

2. Cell Collection

The TransCyt Filter is a biologically neutral membrane that is mounted at one end of the TransCyt Filter cylinder. It has a flat, smooth, porous surface that collects the cells on one plane. A vacuum is applied to the interior of the TransCyt Filter, which collects cells on the exterior surface of the membrane. Cell collection is controlled by software that monitors the pressure across the membrane filter. After collection, the cells sit on one plane over the pores, ready for transfer to a glass slide.

3. Cell Transfer

The natural adhesion properties of cells, pneumatic pressure, and the electrochemical charge of the glass slide are responsible for the transfer of cells from the filter membrane to the glass slide. The cells have a higher affinity for the glass slide than for the membrane. The shape of the TransCyt Filter ensures an evenly distributed, consistently regular circular area of cells on the slide.

IV. Contraindications, Warnings and Precautions

Contraindications

There are no known contraindications for use.

Warnings and Precautions

See attached labeling.

V. Alternative Practices and Procedures

The manual Pap smear is the primary procedure for screening the population for cervical neoplasia or its precursor lesions. It consists of scraping cells from the patient's cervix and manually spreading them onto a glass slide for examination.

VI. Marketing History

Since May 1991, previous and current models of the ThinPrep 2000 Processor have been distributed internationally in Japan, Australia, Italy, Germany, Netherlands, New Zealand, France, Spain, and Canada for both gynecological and nongynecological use. In the U.S., the ThinPrep Processor has been marketed for nongynecological use since 1991.

The ThinPrep 2000 Processor has not been withdrawn from any market for any reason related to safety and effectiveness of the device.

VII. Potential Adverse Effects of the Device on Health

The ThinPrep 2000 Processor, when used to prepare slides for cervical cytology, poses no direct risk and only indirect risk to the patient. There is no direct risk from the ThinPrep 2000

17

Processor because it is not intended for use in therapy or treatment of a patient. The indirect risks include the preparation of slides which may result in false positive or false negative diagnoses.

False positive diagnoses may result when a slide is interpreted as containing abnormalities when no disease is present. As a result, the patient may have an unneccessary colposcopic exam, which is a noninvasive procedure or may be referred for a biopsy, an invasive procedure. False negative diagnoses result in deferred diagnosis or treatment for the patient.

VIII. Summary of Studies

A. Nonclinical Studies

The nonclinical studies were designed to verify that the ThinPrep 2000 Processor slide preparation method is as least as effective as the conventional Pap smear for population screening for the detection of cervical neoplasia and its precursor lesions.

The nonclinical studies evaluated various aspects of the ThinPrep 2000 System, including the ThinPrep 2000 Processor, the TransCyt Filter and PreservCyt solution.

1. ThinPrep 2000 Processor Studies:

The objective of the **Inter-Instrument Variability Study** was to compare the evaluation of specimen adequacy and descriptive diagnosis of slides made from the same set of sample vials on different ThinPrep 2000 Processors in order to establish the variability from instrument to instrument. An acceptable level of inter-instrument variability was achieved: Diagnosis, kappa = 0.93; Specimen Adequacy, kappa = 0.85. The results of the study confirmed the hypothesis that there was no difference between slides produced on different ThinPrep 2000 Processors, and that these slides would be consistent and reproducible between cytology laboratories.

The objective of the **Cross Contamination Study** was to quantify the amount of sample-to-sample cross-contamination present during slide preparation on the ThinPrep 2000 Processor. A low level of cross-contamination between slides was found to occur with the ThinPrep 2000 Processor (mean epithelial count = 1.24 cells). In the cross contamination study no abnormal cells were found to cross-contaminate slides made from abnormal samples on the ThinPrep 2000 Processor.

The objective of the **Intra-Observer Variability Study** was to compare the intra-observer variability, when an individual cytotechnologist screens a slide multiple times, for the descriptive diagnosis evaluation of conventional and ThinPrep slide preparations. There was an acceptable level of agreement among multiple ratings of a ThinPrep slide from one cytotechnologist (kappa = 0.84), and ThinPrep intra-observer variability was comparable to conventional variability.

The objective of the **Inter-Observer Variability Study** was to establish and compare the rates of inter-observer variability for the specimen adequacy and descriptive diagnosis evaluations of

18

conventional Pap smear slides and ThinPrep gynecologic slides. An acceptable level of inter-observer agreement was determined for the ThinPrep slides (average kappa = 0.60), and the level of ThinPrep variability was not significantly different from the level of inter-observer variability determined for the conventional Pap smear slides. The evaluation of ThinPrep slides between cytotechnologists in a screening setting would therefore be relatively consistent and reproducible.

The objective of the **Reproducibility Study** was to demonstrate the reproducibility of the ThinPrep 2000 Processor for making multiple slides from a single cervical sample. The results of the study confirmed the hypothesis that there was no difference in diagnostic presentation for multiple ThinPrep slides made from a single patient sample (kappa = 1.0). This result indicated that a single cytology slide made on a ThinPrep 2000 Processor would be representative of the entire sample collected in PreservCyt solution.

The objective of the **ThinPrep Cell Count Study** was to determine the average number of cells on a ThinPrep slide. The mean cell count for ThinPrep slides was 70,076 cells, and was within the range determined for conventional Pap smears when an equivalent collection device was used (Hutchinson, 1994).

2. TransCyt Filter Studies:

The purpose of the first study, **Cancer Validation Study**, was to demonstrate that cancer cells did not pass through the 8 micrometer polycarbonate TransCyt Filter, and to demonstrate that contextual "background" information useful in the cytologic diagnosis of disease is present on ThinPrep slides. The low flow rates and pressures used in the ThinPrep processes precluded the preferential loss of any particular type of cell. The mean cell diameter for cervical cancer cells has been determined to be 14.7 micrometers for small cell cancer, 15.4 micrometers for endocervical carcinoma and 17.1 micrometers for squamous cell carcinoma.

The results of this study supported the claim that cancer cells and abnormal cells did not pass through the TransCyt Filter during the ThinPrep process.

The purpose of the second study, **TraCit Filter Validation Study**, was to measure the filter retention characteristics of the 8 micrometer pore size TransCyt filter during the slide preparation process on the ThinPrep Processor. This study, using a standard calibrated particle challenge validation methodology, demonstrated that objects greater than 8.1 micrometers did not pass through the TransCyt Filter.

3. PreservCyt Solution Studies:

The objective of the **PreservCyt Shelf-Life Study** was to establish a 12 month shelf-life for PreservCyt Solution. The results of chemical testing of aged PreservCyt Solution that was exposed to simulated shipping conditions or extremes indicated that a stability claim of 12 months was warranted for the shelf life of PreservCyt Solution.

The objective of the **Stability of Cells in PreservCyt Study** was to establish a 3 week claim for the stability of cells stored in PreservCyt Solution. This study demonstrated that

slides made from cells stored for three weeks in PreservCyt Solution, and exposed to temperature extremes during storage, were equivalent to slides made immediately after sample collection in terms of diagnosis and morphology.

B. Clinical Studies

1. Objectives of the Clinical Studies

Three clinical investigations were preformed to determine that slides prepared on the ThinPrep 2000 Processor were as effective as conventional Pap smears in the identification of all categories identified by The Bethesda System for reporting cervical/vaginal diagnoses.

2. Clinical Study #1

a. Study Protocol

A direct comparison of results obtained using ThinPrep 2000 Processor prepared slides and those using conventionally prepared slides was obtained by matched pair study design. A single cervical sample taken from each patient was split into two components: one for a conventional smear, and one for the ThinPrep method. Each conventional and ThinPrep slide was read independently in the laboratory in a blinded manner. This provided an analysis of how each method performed in its intended use.

Following the analysis of the slides at the laboratory, all positive and discrepant cases were sent to a single independent pathologist in order to provide an independent expert cytologic review of the slides, and to provide a standard reference diagnosis for all sites.

b. Objectives of Study #1

The data collected in the first clinical study were analyzed three ways to address the three objectives. (1) To demonstrate equivalence of results of all evaluable positive and negative matched pairs at each clinical site for detection of atypical cells and cervical neoplasia or its precursor lesions. (2) To demonstrate equivalence of results of all evaluable samples positive by ThinPrep and conventional preparation at all clinical sites for detection of atypical cells and cervical neoplasia or its precursor lesions analyzed by the independent pathologist. This analysis gave a more standardized assessment of equivalence of positive results. (3) To demonstrate equivalence all evaluable slides for additional Bethesda System categories.

c. Investigators for Clinical Study #1

This clinical study was performed at six test sites that encompassed a cross section of representative Pap smear screening activity in the United States. Since over 90 percent of Pap smears are typically normal, clinics with high rates of suspected abnormalities were selected at some sites. The investigational sites included a broad spectrum of clinical practice and patient demographics. Three screening centers and three hospital centers took part in the clinical trial. The laboratories and the site pathologist are listed in Table 1.

Table 1. Clinical Study Investigators and Enrollment

	Name and Address of Investigator	Subjects/Samples Enrolled
1.	Karen McIntosh, M.D. Kaiser Regional Laboratory (KRL) Berkeley, CA	1396
2.	Mary Corkill, M.D. Planned Parenthood of the Rocky Mountains (PPR) Denver, CO	1694
3.	Stanley Inhorn, M.D. Wisconsin State Laboratory of Hygiene (WSL) Madison, WI	1099
4.	Kenneth Lee, M.D. Brigham and Women's Hospital (BWH) Boston, MA	1070
5.	George Birdsong, M.D. Grady Memorial Hospital (GMH) Atlanta, GA	1101
6.	Raheela Ashfaq, M.D. Parkland Memorial Hospital (PMH) Dallas, TX	1000

Mark Sherman, M.D., Director of Cytopathology at George Washington University in Washington, D.C., was the independent pathologist.

d. Study Population

Subject Selection and Exclusion Criteria

Eligible patients were enrolled sequentially by the clinician at each site. The single inclusion criterion was female patients 18 years of age or older. Patients were excluded if they had no uterine cervix or if a uterine cervix could not be evaluated.

Sample Size

Sample size was determined prior to initiation of the study based upon data from a feasibility study. A sample size of a minimum of 1,000 patients per investigational site was determined to provide high statistical power. More patients were enrolled at the screening centers in order to ensure adequate statistical power with the anticipated lower prevalence rates at these laboratories.

Of the 7360 patients enrolled into the study, a total of 335 patients/samples were excluded because of inability to pair the ThinPrep and the conventional slide (1), the subjects were under 18 years of age (92), the conventional Pap smear was unsatisfactory (83), the ThinPrep slide was unsatisfactory (106), both slides were unsatisfactory (32), subjects had a hysterectomy (23) or "other" (1).

21

An additional 278 patients/samples were determined to be unevaluable due either to a discrepancy in patient history that could potentially bias the diagnosis or due to inaccurate case report form entries for ThinPrep slides. Therefore, 6747 patients were included in the final primary analysis of this clinical investigation. An additional 3 cases were determined to be unevaluable due to illogical diagnosis from the independent pathologist site. The exclusion and evaluability criteria were determined prior to data analysis.

e. Study Population Demographics

The following tables, 2-5, describe for each investigational site the study parameters, the study population and the site characteristics for the clinical investigation.

Table 2. Duration of Study at Each Investigational Site

Site	Number of Patients Enrolled	Duration of Study (in months)	
KRL	1396	3.25	
PPR	1694	1.5	
WSL	1099	2.75	
BWH	1070	6.0	
GMH	1101	4.5	
PMH	1000	2.75	
Total	7360	6.0	

Table 3. Study Population Summary

Site	Type of Clinical Center	Age Range	Post-Menopausal	Previous Abnormal Pap Smear	Concurrent Infection
KRL	Screening	18.0 - 84.0	10.6%	8.8%	18.6
PPR	Screening	18.0 - 60.6	0.3%	10.7%	7.8
WSL	Screening	18.0 - 48.8	0.0%	7.1%	13.9
BWH	Hospital	18.1 - 89.1	8.1%	40.4%	15.9
GMH	Hospital	18.1 - 84.4	2.1%	18.2%	27.6
PMH	Hospital	18.2 - 78.8	11.1%	38.2%	49.2

Table 4. Race

Site	Caucasian	Asian	Hispanic	African American	Native American	Other	Not Available
KRL	26.3%	6.1%	6.1%	1.8%	0.1%	0.4%	59.2%
PPR	65.4%	1.3%	4.2%	3.2%	0.1%	0.3%	25.6%
WSL	76.7%	0.7%	0.6%	5.1%	0.5%	0.1%	16.4%
BWH	43.9%	2.4%	11.8%	4.5%	6.4%	1.9%	28.6%
GMH	2.5%	1.1%	12.2%	54.3%	0.0%	0.6%	29.4%
PMH	18.3%	1.7%	32.4%	37.1%	0.1%	0.4%	10.0%
Total	41.2%	2.3%	9.7%	15.2%	1.0%	0.6%	30.0%

Table 5. Site Characteristics

Site	Number of Clinicians in Study	Number of Cytotechnologists in Study	Number of Pap Smears per Year
KRL	23	5	300,000
PPR	18	5	100,000
WSL	17	5	96,000
BWH	44	7	35,000
GMH	60	7	40,000
PMH	67	6	37,000

f. Adverse Reactions and Complications

No device related adverse reactions or complications occurred during the clinical investigation or during the supporting clinical studies.

g. Patient Discontinuation

The clinical investigation of the ThinPrep 2000 Processor was conducted using cervical samples collected from patients. No patient follow-up was required and consequently there was no patient discontinuation in the study.

h. Patient Complaints

There were no patient complaints related to the ThinPrep 2000 Processor during the course of this clinical investigation.

i. Device Failures and Replacements

A summary of ThinPrep 2000 Processor failures reported by clinical sites during the clinical investigation is presented in Table 6. There were no device replacements during the clinical investigation.

Table 6. Summary of Device Failures During Clinical Investigation

Failure	Number	Cause	Corrective Action
System 03, Sample too Dense	27	System sensor overly sensitive to sample density	Instrument sensor recalibrated to allow processing
Slide failed to eject	7	Failure due to slide ejector alignment and placement of slide labels	Technical service adjusted slide ejector and instructed site personnel on proper placement of slide
Broken slide	6	Failure due to improper placement of slide in the slide holder	Technical service instructed site personnel on proper slide placement
System 5504 error slide handler did not return to home position	2	Slide handling homing sensor malfunction	Slide handling homing sensor adjusted to allow detection

j. Safety and Effectiveness Data/Results of Clinical Study #1

The clinical study results are presented separately for each of the three analyses of the data: (1) the primary correlations determined by the individual pathologist at each location, (2) the analysis by the single independent pathologist, and (3) the comparison of specimen adequacy using additional categories of The Bethesda System.

(1) Primary Correlation of ThinPrep Results to those Obtained Using Conventional Pap Smears

Table 7 shows the comparison between conventional and ThinPrep findings from clinical study #1 for all of the investigational sites combined. The diagnostic classes for atypical cells and cervical neoplasia and precursor lesions of The Bethesda System were used to present the data in a 7 x 7 classification table. This presentation provides information on the complete range of evaluable diagnoses. Of the 7360 total patients enrolled, 6747 evaluable matched pairs were included in this analysis.

Table 7. 7 x 7 Classification Table for All Sites

		Conventional							
		NEG	ASCUS	AGUS	LSIL	HSIL	SQ CA	GL CA	TOTAL
Thin-Prep	NEG	5224	295	3	60	11	0	0	5593
	ASCUS	318	125	2	45	7	0	0	497
	AGUS	13	2	3	0	1	0	1	20
	LSIL	114	84	0	227	44	0	0	469
	HSIL	11	15	0	35	104	2	0	167
	SQ CA	0	0	0	0	0	1	0	1
	GL CA	0	0	0	0	0	0	0	0
	TOTAL	5680	521	8	367	167	3	1	6747

Abbreviations used in the tables to designate the various Bethesda System Categories: NEG = Normal or negative, ASCUS = Atypical Squamous Cells of Undetermined Significance, AGUS = Atypical Glandular Cells of Undetermined Significance, LSIL = Low-grade Squamous Intraepithelial Lesion, HSIL = High-grade Squamous Intraepithelial Lesion, SQ CA = Squamous Cell Carcinoma, GL CA = Glandular Cell Adenocarcinoma

It can be seen in Table 7 that the ThinPrep method detected more squamous epithelial cell abnormalities than the conventional preparation. Similar numbers of ASCUS and HSIL were found by both methods, but many more LSIL cases were diagnosed with the ThinPrep method. As is typical in the United States' patient population, few cases of cervical cancer were represented in the clinical study. Nonclinical studies have demonstrated the satisfactory performance of the ThinPrep 2000 Processor for the detection of cervical cancer.

The data of Table 7 may be condensed by collapsing the 7 diagnostic categories into 3 containing diagnoses with similar clinical relevance: negative, ASCUS/AGUS (equivocal) and low grade squamous intraepithelial neoplasm plus all higher grade abnormalities (LSIL+) (Positive). Table 8 shows a comparison of the results in Table 7 presented as a 3 x 3 Table (Negative, Equivocal, Positive) for the ThinPrep method vs. the conventional Pap smear results.

Table 8. Three Category Diagnostic Classification Table

		Conventional			
		NEG	ASCUS/AGUS	LSIL+	TOTAL
Thin-Prep	NEG	5224	298	71	5593
	ASCUS/AGUS	331	132	54	517
	LSIL+	125	99	413	637
	TOTAL	5680	529	538	6747

Qualitative data is more amenable to statistical analysis when it can be collapsed into a 2 x 2 table; whereby the sensitivity and specificity of a new test can be analyzed relative to a reference procedure or test. However, because there is no consensus regarding whether the ASCUS/AGUS (equivocal) results should be collapsed into the negative or positive (LSIL+) categories, the clinical study data was collapsed and analyzed both ways to look for differences in results. Tables 9 and 10 present the data in Table 8 with the equivocal ASCUS/AGUS results collapsed in either direction.

Table 9. 2 x 2 Classification Table for ASCUS/AGUS+ for Six Site Pooling

		Conventional		
		NEG	ASCUS/AGUS+	TOTAL
Thin-Prep	NEG	5224	369	5593
	ASCUS/AGUS+	456	698	1154
	TOTAL	5680	1067	6747

Table 10. 2 x 2 Classification Table for LSIL+ for Six Site Pooling

		Conventional		
		NEG/ASCUS/ AGUS	LSIL+	TOTAL
Thin-Prep	NEG/ASCUS/AGUS	5985	125	6110
	LSIL+	224	413	637
	TOTAL	6209	538	6747

In a simple comparison of the results seen in these two 2 x 2 tables, more "positive" slides were identified using the ThinPrep 2000 Processor than using the conventional Pap smear procedure, whether ASCUS/AGUS are collapsed with positive or negative results. A number of off-diagonal discordant results were seen. However, if it were assumed that it would not be possible to screen women with other methods of slide preparation, then it must be assumed that the method yielding the most positive results is the most effective. This also assumes that there were no "false positive results" by either method. It was assumed that any follow-up confirmatory examinations had benefit to the patient.

Statistical Analysis of the Data from Clinical Study #1, Data Analysis (1)

To analyze statistically the null hypothesis that there is no difference between results obtained using the ThinPrep processor and those obtained from conventional Pap smear processed slides, the 3 x 3 categorical classification matrices of ordinal data created using The Bethesda System classification of Negative, ASCUS/AGUS, and Low Grade SIL and Higher obtained at each of the investigational sites was analyzed using the Mann-Whitney D Statistic. This test provides an analysis for data classified into ordinal categories, taking into account matched pair samples. Table 11 shows the results which were variable at different clinical sites.

Table 11. Classification Summary Table for 3 x 3 Analyses at All Sites.

Site	Cases	p-Value	Statistical Power	Reject the Null Hypothesis?
KRL	1,336	0.012	71.5%	Yes
PPR	1,563	<0.001	99.1%	Yes
WSL	1,058	<0.001	99.5%	Yes
BWH	971	<0.001	96.1%	Yes
GMH	1,010	0.080	41.0%	No
PMH	809	0.159	30.0%	No
All Sites	6,747	<0.001	93.5%	Yes

The collapsed 2 x 2 tables obtained at each of the six investigational sites was analyzed using the McNemar statistic. This test provides a chi-squared value, taking into account matched pair samples. A p-value is obtained from the chi-square using two degrees of freedom since two 2 x 2 tables are extracted from the 3 x 3 data. This analysis can be seen in Tables 12 and 13.

Table 12. Classification Summary Table for 2 x 2 Analyses, ASCUS and Higher at All Sites.

Site	Cases	ThinPrep ASCUS+	Convent. ASCUS+	Ratio TP/C	p-Value	Reject the Null Hypothesis?
KRL	1,336	117	93	1.26	0.067	No
PPR	1,563	124	80	1.55	<0.001	Yes
WSL	1,058	123	81	1.52	<0.001	Yes
BWH	971	204	173	1.18	0.007	Yes
GMH	1,010	259	282	0.92	0.360	No
PMH	809	327	359	0.91	0.102	No
All Sites	6,747	1154	1068	1.08	0.012	Yes

Table 13. Classification Summary Table for 2 x 2 Analyses, Low Grade and Higher at All Sites.

Site	Cases	ThinPrep LSIL+	Convent. LSIL+	Ratio TP/C	p-Value	Reject the Null Hypothesis?
KRL	1,336	46	31	1.48	0.027	Yes
PPR	1,563	78	45	1.73	< 0.001	Yes
WSL	1,058	67	40	1.68	<0.001	Yes
BWH	971	125	96	1.30	<0.001	Yes
GMH	1,010	111	130	0.85	0.135	No
PMH	809	210	196	1.07	0.374	No
All Sites	6,747	637	538	1.18	<0.001	Yes

Conclusions Drawn from the Primary Correlation Study

The analysis showed that results obtained from all six clinical sites was not uniform. Since the trend is not consistent at all sites, the results cannot be pooled and must be analyzed individually. Tables 12 and 13 demonstrated the ThinPrep method gave more positive results than conventional preparation methods at all clinical sites except two. At these two clinical sites, there was not a statistically significant difference in the results.

Most labs obtained more positive slides using ThinPrep prepared slides, but different labs obtained more or less benefit from using ThinPrep prepared slides. One lab obtained fewer positive slides with ThinPrep, but the numbers were not statistically significantly different. Each lab must determine for itself if the ThinPrep method will be of benefit.

(2) Data Analysis by the Single Independent Pathologist

Study Objective

This study gives another view on the null hypothesis that there was no difference between results obtained using the ThinPrep 2000 Processor and those obtained from conventional Pap smear processed slides. Following the analysis of the slides at the laboratory, all positive and discrepant cases were sent on to a single independent pathologist in order to provide an independent review of the slides, and to provide one standard for all six clinical sites.

This study did not evaluate test specificity because negative results were not verified. It was assumed that the reference pathologist made no false positive mistakes. For this primary screening test, any sample called positive is worth the clinical follow-up and/or increased surveillance.

Study Population

Following analysis of all slides at each laboratory, all slides positive by either or both preparation method and 5 per cent of concordant negative slides were sent to the single independent pathologist for independent review of the slides. The cases included in this reference analysis were selected from the same 6747 deemed evaluable for the primary analysis less three cases for which the independent pathologist's case report form contained internal inconsistencies in the diagnostic information.

Table 14. Comparative Positivity: Summary Table for All Sites, ASCUS+ Diagnoses

Site	Screen Positive	Confirmed Positives	ThinPrep ASCUS+	Conventional ASCUS+	Ratio TP/C	p-Value	Reject the Null Hypothesis?
KRL	154	92	72	68	1.06	0.900	No
PPR	157	101	85	59	1.44	0.005	Yes
WSL	148	109	95	65	1.46	<0.001	Yes
BWH	234	170	155	143	1.08	0.237	No
GMH	389	171	143	154	0.93	0.330	No
PMH	441	204	190	191	0.99	1.000	No
All Sites	1523	847	740	680	1.09	<0.001	Yes

Overall for ASCUS and higher, the ThinPrep method detected 45 [(85+95)/(65+59)] percent more positives than the conventional method at two sites and was equivalent at four sites.

Table 15. Comparative Positivity: Summary Table for All Sites, LSIL+ Diagnoses

Site	Screen Positive	Confirmed Positives	ThinPrep LSIL+	Conventional LSIL+	Ratio TP/C	p-Value	Reject the Null Hypothesis?
KRL	52	50	33	25	1.32	0.170	No
PPR	94	65	48	33	1.45	0.042	Yes
WSL	74	77	54	33	1.63	<0.001	Yes
BWH	135	116	102	81	1.26	<0.001	Yes
GMH	161	115	86	90	0.96	0.876	No
PMH	246	126	190	112	1.07	0.170	No
All Sites	762	549	513	374	1.37	<0.001	Yes

Overall for LSIL and higher, the ThinPrep method detected 39 [(48+54+102)/(33+33+81)] percent more positives than the conventional method at three sites and was equivalent at three sites.

Statistical Analysis of the Data from Clinical Study #1, Data Analysis (2)

A single independent pathologist was used as a "gold-standard" for confirming the positive results for the conventional and ThinPrep methods at each of the six clinical sites. A chi-squared value was determined from the McNemar statistic that considered matched pair samples. A p-value was obtained from the McNemar chi-square using two degrees of freedom. The p value showed whether the null hypothesis that the two methods of slide preparation were equivalent or not was accepted or rejected. The ratio of ThinPrep to conventional slide preparation indicated which test enabled the independent pathologist to find the most positive results. Tables 13 and 14 present these results.

Conclusions Drawn from the Confirmatory Analysis by the Independent Pathologist:

This analysis confirmed the results of the primary correlation study that all six clinical sites did not show the same trend in results. Since the trend was not consistent at all sites, these results could not be pooled and must be analyzed individually. Tables 14 and 15 demonstrated the ThinPrep method gave more positive results than the conventional preparation method at all clinical sites except two. These results showed the same trends as the primary screening study, except that the independent pathologist confirmed fewer positive samples prepared by both methods. The same conclusion could be drawn in this study as with the primary screening study. Most labs obtained more positive slides using ThinPrep prepared slides, but some labs may obtain more or less benefit from using ThinPrep prepared slides. One lab obtained fewer positive slides with the ThinPrep System, but this result did not show a statistically significant difference.

The ratio of ThinPrep to conventionally prepared positive slides decreased in most of the clinical sites when the independent pathologist's diagnosis was used. However, in most cases, it did not change significantly. Both ratios were relative to the comparison study chosen, and should be labeled as such. True clinical sensitivity cannot be obtained by any reference method available today due to the subjective nature of interpreting diagnoses and the errors associated with sampling of the cervix. Each lab will have to determine for itself whether or not the ThinPrep method will be of benefit.

(3) Specimen Adequacy Analysis

Study Objective

To demonstrate that slides prepared with the ThinPrep 2000 Processor were as adequate as those prepared by conventional methods when additional diagnoses from The Bethesda System were considered.

Study Population

Of the 7360 total patients/samples in the clinical study, 7223 were included in this specimen adequacy analysis. The samples considered for specimen adequacy were taken from the entire data set to include unsatisfactory samples also. Only cases with incorrect paperwork, age less than 18, or hysterectomy were excluded from this analysis.

Statistical Analysis

The Mann-Whitney D Statistic was used for the analysis of the 3 x 3 tables to determine if the null hypothesis that ThinPrep slides were as adequate as conventionally prepared slides was accepted or rejected. The Mann Whitney D Statistic provides an analysis for data classified into ordinal categories, taking matched pair samples into account.

Study Results

All categories of The Bethesda System of reporting of cytology results were considered in this third analysis of information of the primary clinical study. The Bethesda System categories were condensed to the following three categories to evaluate the data obtained from the clinical study: "Satisfactory," "Satisfactory But Limited By ... (SBLB)," and "Unsatisfactory." These three categories were used in 3 x 3 tables to show a paired comparison between samples taken and split between ThinPrep and conventional preparation techniques. Table 16 summarizes these overall results from all six clinical sites combined.

Table 16. 3 x 3 Specimen Adequacy Table for All Sites in the Clinical Study.

		Conventional			
		SAT	SBLB	UNSAT	TOTAL
Thin-Prep	SAT	4316	1302	38	5656
	SBLB	722	665	44	1431
	UNSAT	63	41	32	136
	TOTAL	5101	2008	114	7223

Conclusions: The Mann-Whitney D Statistic was 0.075 with a p value of <0.001 and statistical power of 100 percent. This indicated that the null hypothesis is rejected, and it can be inferred that the two methods were not equivalent. As can be seen in the 3 x 3 table, the ThinPrep had 19 percent (136/114) more unsatisfactory results than conventional methods. On the other hand, the conventional method had 40 percent more (2008/1431) "Unsatisfactory But Limited By ..." results than the ThinPrep.

Table 17 presents the data included in Table 16 for each of the six individual clinical sites.

Table 17. Classification Summary Table for 3 x 3 Analyses of Specimen Adequacy at All Sites.

Site	Cases	p-Value	Reject the Null Hypothesis?	Method Favored
KRL	1,386	< 0.001	Yes	CP
PPR	1,668	<0.001	Yes	TP
WSL	1,093	<0.001	Yes	TP
BWH	1,046	<0.001	Yes	TP
GMH	1,049	0.375	No	Neither
PMH	981	< 0.001	Yes	TP
All Sites	7,223	<0.001	Yes	TP

31

Conclusions: The results were not uniform at all sites, and thus should not be pooled. Overall, four sites had more satisfactory results with the ThinPrep method, one site favored the conventionally prepared slides, while one site showed equivalent results (GMH).

Table 18 shows the rates of detection for SBLB results of infection, reactive changes and the total benign cellular changes for both the ThinPrep and conventional methods at all sites.

Table 18. Marginal Frequencies for Benign Cellular Changes for All Sites.

Descriptive Diagnosis	ThinPrep		Conventional	
	N	%	N	%
Infection	1392	20.6	1348	20.0
Reactive Changes	412	6.1	471	7.0
Total Benign Cellular Changes	1592	23.6	1591	23.6

Note: Some patients may have had both an infection and reactive cellular change.

Conclusions: Results appeared comparable for the two methods.

More glandular cell abnormalities including AGUS and benign endometrial cells in postmenopausal women were detected on ThinPrep slides (49 vs. 29) than on conventionally prepared slides.

The SBLB category can be broken down into a number of important subcategories. One of the most important of SBLB subcategories is "Absence of Endocervical Component." The presence of endocervical component is a very important criteria for slide adequacy.

Table 19. SBLB Rates for no Endocervical Component (ECC), All Six Sites.

SBLB Due to No ECC's				
Site	ThinPrep SBLB-no ECC's	ThinPrep SBLB-no ECC's (%)	Conventional SBLB-no ECC's	Conventional SBLB-no ECC's (%)
KRL	237	17.1%	162	11.7%
PPR	104	6.2%	73	4.4%
WSL	145	13.3%	84	7.7%
BWH	229	21.9%	115	11.0%
GMH	305	29.1%	150	14.3%
PMH	120	12.2%	97	9.9%
All Sites	1140	15.8%	681	9.4%

Conclusions: As can be seen in Table 19, there was a consistent trend at all six clinical sites. ThinPrep prepared slides were deficient in endocervical components at all six sites.

1750

These data showed that over all six clinical sites, ThinPrep prepared slides had no endocervical component in 6.4 percent more cases than conventional preparation methods. The applicant speculated that this could have been caused by the fact that the conventional slide was prepared first, then the sampling device was rinsed into the PreservCyt solution. The applicant speculated that this could bias results in favor of conventionally prepared slides. To investigate this possibility further, the applicant set up two additional supporting clinical studies to show that when cervical samples were placed directly into the PreservCyt Solution, as will be done in actual use, that the detection of endocervical component was equivalent to conventionally prepared slides on the average.

3. Supporting Clinical Studies #2 and #3

a. Objectives of Supporting Clinical Studies #2 and #3

Two clinical investigations were performed to demonstrate that when used as intended, the ThinPrep slides were equivalent to conventionally prepared slides with respect to adequacy of slides as judged by presence of endocervical component. Study #2 was a feasibility study to provide a preliminary assessment. Study #3 was a larger study.

b. Background for Supporting Clinical Studies #2 and #3.

Clinical Study #1 showed an overall 6.4 percent spread between conventional and ThinPrep methods in detecting endocervical component. The applicant speculated that the collection of adequate endocervical component may have been compromised by the split sample collection technique used for matched pair statistical analysis. To test this hypothesis two clinical studies were performed with samples rinsed directly into the PreservCyt vials according to the ThinPrep intended use. Direct-to-Vial ThinPrep results were compared to specimen adequacy results of conventional Pap smear slides for broom collection devices found in clinical study #1.

c. Investigators for the Direct to Vial Supportive Studies

The principle investigator of Study #2, the feasibility study was, Martha Hutchinson, Ph.D., M.D. of the New England Medical Center (NEMC) in Boston, MA.

The principal investigator of Study #3 was Mary Corkill, M.D. of Planned Parenthood of the Rocky Mountains (PPRM) in Denver, CO.

d. Study Populations

Supporting Clinical Study #2

A total of 299 women were enrolled. Each woman provided one sample. It was estimated that 299 women would provide sufficient numbers to detect large differences compared to published specimen adequacy rates of conventional Pap smear slides for broom collection devices. Included were women 18 years of age or older. Samples were taken at a time outside of their normal Pap smear regimen. Excluded were women without a uterine cervix and women in whom a uterine cervix could not be visualized by the clinician. All women enrolled were evaluable.

Supporting Clinical Study #3

A total of 499 women were enrolled. Each woman provided one sample. The sample size was calculated according to standard methods assuming that the test samples have 94 per cent of endocervical cell positive ThinPrep slides rather than typical published results for conventional smears using broom collection devices (90 per cent endocervical cell positive). For the one sided test with alpha = 0.05 and 95 per cent power, n was equal to 489. Included were females 18 years of age or older. Subjects were volunteers. Samples were taken in addition to their normal Pap smear screening regimen. Excluded were women without a uterine cervix and women in whom a uterine cervix could not be visualized by the clinician and women who were enrolled in the study more than once.

Of the 499 enrolled patients, 484 (97 per cent) were evaluable. One (1) subject was younger than 18 years, 9 had hysterectomies, and 5 subjects were previously enrolled.

e. Safety and Effectiveness Data/Results of Direct-to-Vial Supporting Clinical Studies

The results of Supporting Clinical Studies #2 and #3 are summarized in Table 20

Table 20. Summary of Direct-to-Vial Studies.

Study	Number of Evaluable Patients	SBLB due to No Endocervical Component	Comparable Conventional Pap Smear Percentage
Direct-to-Vial Feasibility	299	9.36% (28/299) (6.3-13.3%)	9.4%[a] (681/7223) (8.75-10.1%)
Direct-to-Vial Clinical Study	484	4.96% (24/484) (3.2-7.3%)	4.4%[b] (73/1668) (3.45-5.47%)

a. Direct-to-Vial Feasibility study compared to overall clinical investigation conventional Pap smear SBLB- No Endocervical Component rate.

b. Direct-to-Vial clinical study compared to site PPR clinical investigation conventional Pap smear SBLB-No Endocervical Component rate.

Supporting Clinical Study #2

Twenty-eight of the 299 total samples (9.4 per cent) were " Satisfactory but Limited By No Endocervical Component." This figure was compared to the 9.4 per cent of "Satisfactory But Limited By No Endocervical Component" found for the conventional Pap smear using the broom type sampling device for all 7223 evaluable slides during the primary clinical study #1.

Supporting Clinical Study #3

Twenty-four of 484 (5.0 percent) total samples were "Satisfactory but Limited By No Endocervical Component". This figure was compared to the 4.4 per cent of "Satisfactory But Limited By No Endocervical Component" found for the conventional Pap smear using the broom type sampling device at the same clinical site during the primary clinical study #1

Statistical Analysis of the Data from Supporting Clinical Studies #2 and #3

Satisfactory overlap of 95 per cent confidence intervals with values was used to determine if the results found in the different studies were equivalent. As can be seen in Table 20, satisfactory overlap of confidence intervals occurred.

f. Conclusions:

Both supporting studies showed no difference between ThinPrep and selected studies of the conventional Pap smear method in the percentage of "Satisfactory But Limited By No Endocervical Component" when the ThinPrep was used as intended and the sample was placed directly in the PreservCyt vial.

C. Statement of Regulatory Compliance

The clinical studies were conducted in compliance with the Institutional Review Board (IRB) regulations in 21 CFR Part 56, and in compliance with the informed consent regulations in 21 CFR Part 50.

The investigational device was determined to be a nonsignificant risk device by each reviewing IRB. As a nonsignificant risk device, the ThinPrep 2000 Processor was exempt from the requirements for submission of a Investigational Device Exemption (IDE) application as specified in 21 CFR Part 812. The clinical investigation was in compliance with all other IDE regulation requirements for nonsignificant risk devices.

31

The responsibility for monitoring, data management and quality assurance of the clinical investigation was transferred by the applicant to a Contract Research Organization (CRO). The CRO was Medical and Technical Research Associates (MTRA) of Wellesley, Massachusetts. The specific obligations of the CRO were stated in writing prior to initiation of the study. The applicant and an independent Quality Assurance consultant monitored and audited the conduct of the CRO to assure compliance with the IDE regulations.

IX. Conclusions Drawn from Studies

The applicant has shown that cytotechnologists and pathologists using thin-layer cytologic slides prepared by the ThinPrep 2000 Processor detected equivalent numbers of The Bethesda System positive events compared to when the same cytotechnologists and pathologists read conventionally prepared Pap smear preparations.

A. Nonclinical Supporting Studies:

The nonclinical supporting studies provided valid scientific evidence of the accuracy, precision, morphologic preservation and presentation and stability of reagents. Each nonclinical study had a clearly defined objective and, when appropriate, a hypothesis. Efforts were taken to minimize potential bias in each study.

B. Discussion of Valid Scientific Evidence

The clinical investigation constituted valid scientific evidence as defined in 21 CFR 860.7. The investigation was well-controlled in that a test article and control article were made from each study subject's cervical sample. This was possible by using a split-sample collection methodology in which a conventional Pap smear was first made, and then the collection device was rinsed in PreservCyt solution. The ThinPrep slide was then made from the sample in PreservCyt solution.

The clinical investigation protocol included a statement of the objectives and hypotheses of the study. Statistical testing was based on these pre-defined hypotheses. The clinical sites were monitored by an independent Contract Research Organization to assure adherence to the protocol.

The statistical methods used to analyze the data from this investigation were based on FDA recommendations contained in *Points to Consider for Cervical Cytology Devices.* All hypothesis testing was done at $\alpha = 0.05$. The statistical power was a minimum of 93.5 percent for the analyses conducted on the combined data from all clinical sites. Two separate analyses were conducted. The primary analysis included only evaluable patients, a secondary analysis included all patients. Data management and statistical analyses were conducted by an independent Contract Research Organization using industry-standard data verification and validation methodologies.

C. Discussion of Data on Safety and Effectiveness

Clinical tests on 7530 evaluable women assessed the safety and effectiveness of the ThinPrep 2000 Processor as a slide preparation device. Supporting tests assessed its specific performance characteristics and reagent stability. These studies supported the following conclusions:

- Results from the primary clinical study #1 did not show the same trends at all six clinical sites. Therefore the data from all six clinical sites cannot be pooled.

- When only LSIL or higher diagnoses were considered positive, the site pathologists and the independent pathologist analysis found more positive slides reading the ThinPrep prepared slides than the conventional cytology method at four investigational sites. The methods were equivalent at two sites.

When equivocal ASCUS/AGUS diagnoses were grouped with LSIL or higher diagnoses, the site pathologists reading ThinPrep prepared slides found more positive slides than with the conventional cytology method at three investigational sites. The methods were equivalent at three sites.

When equivocal ASCUS/AGUS diagnoses were grouped with LSIL or higher diagnoses, the independent pathologist found more positive slides reading the ThinPrep slides than were found with the conventional cytology method at only two investigational sites. The methods were equivalent at four sites.

The specimen adequacy study showed variable results depending on how the data was analyzed.

When analyzed by site, overall results varied from lab to lab. More adequate samples were obtained using the ThinPrep method than the conventional cytology method at four investigational sites. Results were equivalent at one site. More adequate samples were seen using conventional Pap smears at one investigational site.

For the specimen adequacy data from all six sites, more slides were designated as Satisfactory with no limiting factors using the ThinPrep method than the conventional cytology method (5656 ThinPrep slides versus 5101 conventional Pap smears). Also, fewer ThinPrep slides were "Satisfactory But Limited By ..." (1431 ThinPrep slides versus 2008 conventional pap slides). However, there were more Unsatisfactory ThinPrep slides (136 ThinPrep slides versus 114 conventional Pap smears).

The analysis showed 69 percent more (49/29) glandular cell abnormalities including AGUS and benign endometrial cells in postmenopausal women on ThinPrep slides than on the conventional Pap smear slides.

When compared to the corresponding conventional smears, the ThinPrep 2000 Processor preparation showed an equivalent detection of Benign Cellular Changes.

When samples were placed directly into the vial of PreservCyt Solution there was no difference in endocervical component between the ThinPrep method and the conventional Pap smear method.

D. General Conclusions from the Studies

Data from the clinical and nonclinical studies demonstrated that the ThinPrep 2000 Processor was at least as safe and effective as the conventional Pap smear method for preparing cervical cytology samples for detecting all categories of The Bethesda System in all laboratories in the clinical studies. Nonclinical studies demonstrated that ThinPrep prepared slides were reproducible and uniform. The results showed that the that the device was able to preserve and present the cell sample onto a controlled area of the slide, randomize the sampling of the cells harvested from the women without selective cell loss, and preserve the contextual information, diathesis, and infectious agents.

CDRH has concluded that the device is safe and effective for its intended use.

E. Risk/Benefit Analysis

The results of the clinical investigation demonstrated that cervical cytology slides prepared with the ThinPrep 2000 Processor gave the same results as the conventional Pap smear for the detection of cervical neoplasia and its precursor lesions. The conventional Pap smear is the only alternative procedure for screening for cervical neoplasia and its precursor lesions. The ThinPrep 2000 Processor does not contact the patient and it uses samples collected by the same methods, with minimal associated physical risks. Therefore, with detection of disease and equivalent physical risks to the patient, the Risk/Benefit ratio of the ThinPrep 2000 Processor method was equivalent to the conventional Pap smear.

X. Panel Recommendation

The Hematology and Pathology Device Panel recommended at the panel meeting on June 7, 1993 that the PMA for the ThinPrep Processor, Beta model (P920009), be approved. On March 22, 1994, the PMA was withdrawn at the request of Cytyc Corporation. Additional studies with the ThinPrep Processor, Model TP 2000 were performed. After completing these additional studies Cytyc Corporation resubmitted the PMA which was filed on November 22, 1995.

XI. CDRH Action on the Application

CDRH issued an approval order for applicant's PMA for the ThinPrep Processor, Model TP 2000 to Cytyc Corporation on May 20, 1996.

The applicant's manufacturing and control facilities were inspected on February 28, 1996 and the facilities were found to be in compliance with the Good Manufacturing Practiced Regulations (GMPs).

XII. Approval Specifications

Directions for use: See attached labeling.

Conditions of Approval: CDRH approval of this PMA is subject to full compliance with the conditions described in the approval order.

XIII. Bibliography

Hutchinson M, Isenstein L, Goodman A, Hurley A, Mui K, Patten F, Zahniser D: Homogeneous sampling accounts for the increased diagnostic accuracy using the ThinPrep Processor, Am J Clin Pathol 101:1-7, 1994

Koss L: The Papanicolaou test for cervical cancer detection: A triumph and a tragedy, JAMA 261:737-743, 1989

Kurman RJ, Soloman D: The Bethesda System for Reporting Cervical/Vaginal Cytologic Diseases, Springer-Verlag, New York, 1994.

Labeling

Cytyc Corporation
ThinPrep® 2000 System

INDICATION FOR USE

INTENDED USE

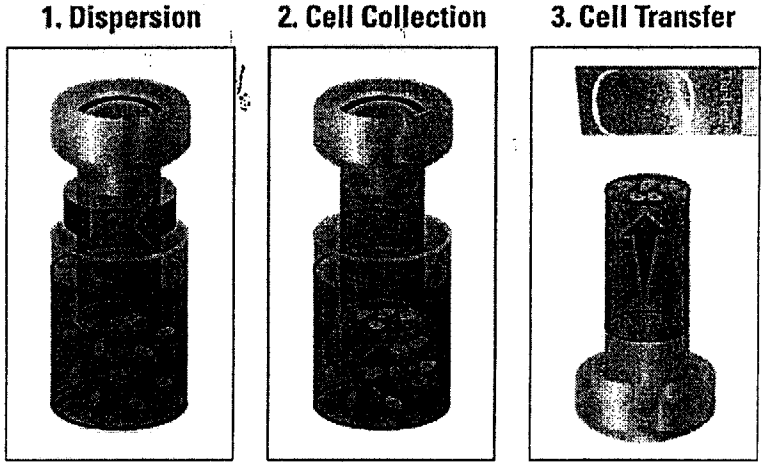
The ThinPrep® 2000 System is intended as a replacement for the conventional method of Pap smear preparation for use in screening for the presence of atypical cells, cervical cancer, or its precursor lesions (Low Grade Squamous Intraepithelial Lesions, High Grade Squamous Intraepithelial Lesions), as well as all other cytologic categories as defined by *The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses*[1].

SUMMARY AND EXPLANATION OF THE SYSTEM

The ThinPrep process begins with the patient's gynecologic sample being collected by the clinician using a broom-type cervical sampling device which, rather than being smeared on a microscope slide, is immersed and rinsed in a vial filled with PreservCyt Solution. The ThinPrep sample vial is then capped, labeled, and sent to a laboratory equipped with a ThinPrep 2000 Processor.

At the laboratory, the PreservCyt® sample vial is placed into a ThinPrep 2000 Processor and a gentle dispersion step breaks up blood, mucus, non-diagnostic debris, and thoroughly mixes the cell sample. The cells are then collected on a TransCyt® Filter specifically designed to collect diagnostic cells. The ThinPrep 2000 Processor constantly monitors the rate of flow through the TransCyt Filter during the collection process in order to prevent the cellular presentation from being too scant or too dense. A thin layer of cells is then transferred to a glass slide in a 20 mm-diameter circle, and the slide is automatically deposited into a fixative solution.

The ThinPrep Sample Preparation Process



(1) Dispersion

The TransCyt Filter rotates within the sample vial, creating currents in the fluid that are strong enough to separate debris and disperse mucus, but gentle enough to have no adverse effect on cell appearance.

(2) Cell Collection

A gentle vacuum is created within the TransCyt Filter, which collects cells on the exterior surface of the membrane. Cell collection is controlled by the ThinPrep 2000 Processor's software that monitors the rate of flow through the TransCyt Filter.

(3) Cell Transfer

After the cells are collected on the membrane, the TransCyt Filter is inverted and gently pressed against the ThinPrep Microscope Slide. Natural attraction and slight positive air pressure cause the cells to adhere to the ThinPrep Microscope Slide resulting in an even distribution of cells in a defined circular area.

As with conventional Pap smears, slides prepared with the ThinPrep 2000 System are examined in the context of the patient's clinical history and information provided by other diagnostic procedures such as colposcopy, biopsy, and human papillomavirus (HPV) testing, to determine patient management.

LIMITATIONS

- Gynecologic samples collected for preparation using the ThinPrep 2000 System should be collected using a broom type collection device.
- Preparation of microscope slides using the ThinPrep 2000 System should be performed only by personnel who have been trained by Cytyc Corporation or by organizations or individuals designated by Cytyc Corporation.
- Evaluation of microscope slides produced with the ThinPrep 2000 System should be performed only by cytotechnologists and pathologists who have been trained to evaluate ThinPrep prepared slides by Cytyc Corporation or by organizations or individuals designated by Cytyc Corporation.
- Supplies used in the ThinPrep 2000 System are those designed and supplied by Cytyc Corporation specifically for the ThinPrep 2000 System. These include PreservCyt Solution vials, TransCyt Filters, and ThinPrep Microscope Slides. These supplies are required for proper performance of the system and cannot be substituted. Product performance will be compromised if other supplies are used. After use, supplies should be disposed of in accordance with local, state, and federal regulations.
- A TransCyt Filter must be used only once and cannot be reused.

WARNINGS

- PreservCyt Solution contains methanol which is poisonous and may be fatal or cause blindness if swallowed. Methanol vapor may be harmful. PreservCyt is flammable; keep away from fire, heat, sparks, and flame. Other solutions must not be substituted for PreservCyt solution. PreservCyt Solution should be stored and disposed of in accordance with local, state, and federal regulations.

PRECAUTIONS

- This equipment generates, uses and can radiate radio frequency energy, and if not installed and used in accordance with the Operator's Manual, . . may cause interference to radio communications. Operation of this equipment in a residential area is likely to cause harmful interference, in which case the user will be required to correct the interference at his/her own expense.
- The storage limit for cells in PreservCyt is 3 weeks at 4° to 37°C
- PreservCyt Solution is bactericidal. PreservCyt Solution has been shown to cause greater than 99.999 percent inactivation within 15 minutes for the following bacteria: *Candida albicans, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Mycobacterium tuberculosis*. As with all laboratory procedures, universal precautions should be followed.

PERFORMANCE CHARACTERISTICS: REPORT OF CLINICAL STUDIES

A prospective multi-center clinical study was conducted to evaluate the performance of the ThinPrep 2000 System in direct comparison to the conventional Pap smear. The objective of the ThinPrep clinical study was to demonstrate that gynecologic specimens prepared using the ThinPrep 2000 System were at least as effective as conventional Pap smears for the detection of atypical cells and cervical cancer or its precursor lesions in a variety of patient populations. In addition, an assessment of specimen adequacy was performed.

The initial clinical study protocol was a blinded, split sample, matched pair study, for which a conventional Pap smear was prepared first, and the remainder of the sample (the portion that normally would have been discarded) was immersed and rinsed into a vial of PreservCyt Solution. At the laboratory, the PreservCyt sample vial was placed into a ThinPrep 2000 Processor and a slide was then prepared from the patient's sample. ThinPrep and conventional Pap

smear slides were examined and diagnosed independently. Reporting forms containing patient history as well as a checklist of all possible categories of The Bethesda System were used to record the results of the screening. A single independent pathologist reviewed all discrepant and positive slides from all sites in a blinded fashion to provide a further objective review of the results.

LABORATORY AND PATIENT CHARACTERISTICS

Cytology laboratories at three screening centers (designated as S1, S2, and S3) and three hospital centers (designated as H1, H2, and H3) participated in the clinical study. The screening centers in the study serve patient populations (screening populations) with rates of abnormality (Low Grade Squamous Intraepithelial Lesion, [LSIL], and more severe lesions) similar to the United States average of less than 5%.[2] The hospital centers in the study serve a high risk referral patient population (hospital populations) characterized by high rates (>10%) of cervical abnormality. Data on race demographics was obtained for 70% of the patients that participated in the study. The study population consisted of the following race groups: Caucasian (41.2%), Asian (2.3%), Hispanic (9.7%), African American (15.2%), Native American (1.0%) and other groups (0.6%). Table 1 describes the laboratories and the patient populations.

Table 1: Site Characteristics

Laboratory Characteristics			Clinical Study Demographics				
Site	Type of Patient Population	Laboratory Volume - Smears per Year	Cases	Patient Age Range	Post-Meno-pausal	Previous Abnormal Pap Smear	Convent. Prevalence LSIL+
S1	Screening	300,000	1,386	18.0 - 84.0	10.6%	8.8%	2.3%
S2	Screening	100,000	1,668	18.0 - 60.6	0.3%	10.7%	2.9%
S3	Screening	96,000	1,093	18.0 - 48.8	0.0%	7.1%	3.8%
H1	Hospital	35,000	1,046	18.1 - 89.1	8.1%	40.4%	9.9%
H2	Hospital	40,000	1,049	18.1 - 84.4	2.1%	18.2%	12.9%
H3	Hospital	37,000	981	18.2 - 78.8	11.1%	38.2%	24.2%

CLINICAL STUDY RESULTS

The diagnostic categories of The Bethesda System were used as the basis of the comparison between conventional and ThinPrep findings from the clinical study. The diagnostic classification data and statistical analyses for all clinical sites are presented in Tables 2 through 11. Cases with incorrect paperwork, patient's age less than 18 years, cytologically unsatisfactory slides, or patients with a hysterectomy were excluded from this analysis. Few cases of cervical cancer (0.02% [3]) were represented in the clinical study, as is typical in the United States patient population.

Table 2: Diagnostic Classification Table, All Categories

		Conventional							
		NEG	ASCUS	AGUS	LSIL	HSIL	SQ CA	GL CA	TOTAL
Thin-Prep	NEG	5224	295	3	60	11	0	0	5593
	ASCUS	318	125	2	45	7	0	0	497
	AGUS	13	2	3	0	1	0	1	20
	LSIL	114	84	0	227	44	0	0	469
	HSIL	11	15	0	35	104	2	0	167
	SQ CA	0	0	0	0	0	1	0	1
	GL CA	0	0	0	0	0	0	0	0
	TOTAL	5680	521	8	367	167	3	1	6747

Abbreviations for Diagnoses: NEG = Normal or negative, ASCUS = Atypical Squamous Cells of Undetermined Significance, AGUS = Atypical Glandular Cells of Undetermined Significance, LSIL = Low-grade Squamous Intraepithelial Lesion, HSIL = High-grade Squamous Intraepithelial Lesion, SQ CA = Squamous Cell Carcinoma, GL CA = Glandular Cell Adenocarcinoma.

Table 3: Three Category Diagnostic Classification Table

		Conventional			
		NEG	ASCUS/ AGUS	LSIL+	TOTAL
Thin-Prep	NEG	5224	298	71	5593
	ASCUS/AGUS	331	132	54	517
	LSIL+	125	99	413	637
	TOTAL	5680	529	538	6747

Table 4: Two Category Diagnostic Classification Table, LSIL and More Severe Diagnoses

		Conventional		
		NEG/ASCUS/ AGUS	LSIL+	TOTAL
Thin-Prep	NEG/ASCUS/AGUS	5985	125	6110
	LSIL+	224	413	637
	TOTAL	6209	538	6747

Table 5: Two Category Diagnostic Classification Table, ASCUS/AGUS and More Severe Diagnoses

		Conventional		
		NEG	ASCUS/AGUS+	TOTAL
Thin-Prep	NEG	5224	369	5593
	ASCUS/AGUS+	456	698	1154
	TOTAL	5680	1067	6747

The diagnostic data analysis from the sites is summarized in Tables 6 and 7. When the p-value is significant ($p < 0.05$), the method favored is indicated in the tables.

Table 6: Results by Site, LSIL and More Severe Lesions

Site	Cases	ThinPrep LSIL+	Convent LSIL+	Increased Detection*	p-Value	Method Favored
S1	1,336	46	31	48%	0.027	ThinPrep
S2	1,563	78	45	73%	<0.001	ThinPrep
S3	1,058	67	40	68%	<0.001	ThinPrep
H1	971	125	96	30%	<0.001	ThinPrep
H2	1,010	111	130	(15%)	0.135	Neither
H3	809	210	196	7%	0.374	Neither

*Increased detection = $\frac{\text{ThinPrep LSIL+ - Conventional LSIL+}}{\text{Conventional LSIL+}} \times 100\%$

For LSIL and more severe lesions, the diagnostic comparison statistically favored the ThinPrep method at four sites and was statistically equivalent at two sites.

Table 7: Results by Site, ASCUS/AGUS and More Severe Lesions

Site	Cases	ThinPrep ASCUS+	Convent. ASCUS+	Increased Detection	p-Value	Method Favored
S1	1,336	117	93	26%	0.067	Neither
S2	1,563	124	80	55%	<0.001	ThinPrep
S3	1,058	123	81	52%	<0.001	ThinPrep
H1	971	204	173	18%	0.007	ThinPrep
H2	1,010	259	282	(8%)	0.360	Neither
H3	809	327	359	(9%)	0.102	Neither

*Increased detection = $\frac{\text{ThinPrep LSIL+ - Conventional LSIL+}}{\text{Conventional LSIL+}} \times 100\%$

For ASCUS/AGUS and more severe lesions, the diagnostic comparison statistically favored the ThinPrep method at three sites and was statistically equivalent at three sites.

One pathologist served as an independent reviewer for the six clinical sites, receiving both slides from cases where the two methods were either abnormal or discrepant. Since a true reference cannot be determined in such studies and therefore true sensitivity cannot be calculated, the use of an expert cytologic review provides an alternative to histologic confirmation by biopsy or human papillomavirus (HPV) testing as a means for determining the reference diagnosis.

The reference diagnosis was the more severe diagnosis from either of the ThinPrep or conventional Pap slides as determined by the independent pathologist. The number of slides diagnosed as abnormal at each site, compared to the reference diagnosis of the independent pathologist, provides the proportion of LSIL or more severe lesions (Table 8) and the proportion of ASCUS/AGUS or

more severe lesions (Table 9). The statistical analysis allows a comparison of the two methods and a determination of which method is favored when using the independent pathologist for expert cytologic review as the adjudicator of the final diagnosis.

Table 8: Independent Pathologist Results by Site, LSIL and More Severe Lesions

Site	Cases	ThinPrep Positive	Conventional Positive	p-Value	Method Favored
S1	50	33	25	0.170	Neither
S2	65	48	33	0.042	ThinPrep
S3	77	54	33	<0.001	ThinPrep
H1	116	102	81	<0.001	ThinPrep
H2	115	86	90	0.876	Neither
H3	126	120	112	0.170	Neither

For LSIL and more severe lesions, the diagnostic comparison statistically favored the ThinPrep method at three sites and was statistically equivalent at three sites.

Table 9: Independent Pathologist Results by Site, ASCUS/AGUS and More Severe Lesions

Site	Cases	ThinPrep Positive	Conventional Positive	p-Value	Method Favored
S1	92	72	68	0.900	Neither
S2	101	85	59	0.005	ThinPrep
S3	109	95	65	<0.001	ThinPrep
H1	170	155	143	0.237	Neither
H2	171	143	154	0.330	Neither
H3	204	190	191	1.000	Neither

For ASCUS/AGUS and more severe lesions, the diagnostic comparison statistically favored the ThinPrep method at two sites and was statistically equivalent at four sites.

Table 10 below shows the summary for all sites of the descriptive diagnosis for all Bethesda System categories.

Table 10: Summary of Descriptive Diagnosis

Descriptive Diagnosis *Number of Patients: 6747*	ThinPrep N	ThinPrep %	Conventional N	Conventional %
Benign Cellular Changes:	**1592**	**23.6**	**1591**	**23.6**
Infection:				
Trichomonas Vaginalis	136	2.0	185	2.7
Candida spp.	406	6.0	259	3.8
Coccobacilli	690	10.2	608	9.0
Actinomyces spp.	2	0.0	3	0.0
Herpes	3	0.0	8	0.1
Other	155	2.3	285	4.2
Reactive Cellular Changes Associated with:				
Inflammation	353	5.2	385	5.7
Atrophic Vaginitis	32	0.5	48	0.7
Radiation	2	0.0	1	0.0
Other	25	0.4	37	0.5
Epithelial Cell Abnormalities:	**1159**	**17.2**	**1077**	**16.0**
Squamous Cell:				
ASCUS	501	7.4	521	7.7
favor reactive	128	1.9	131	1.9
favor neoplastic	161	2.4	140	2.1
undetermined	213	3.2	250	3.7
LSIL	469	7.0	367	5.4
HSIL	167	2.5	167	2.5
Carcinoma	1	0.0	3	0.0
Glandular Cell:				
Benign Endometrial cells in Postmenopausal Women	7	0.1	10	0.1
Atypical Glandular Cells (AGUS)	21	0.3	9	0.1
favor reactive	9	0.1	4	0.1
favor neoplastic	0	0.0	3	0.0
undetermined	12	0.2	2	0.0
Endocervical Adenocarcinoma	0	0.0	1	0.0

Note: Some patients had more than one diagnostic subcategory.

Table 11 shows the rates of detection for infection, reactive changes, and the total benign cellular changes for both the ThinPrep and conventional methods at all sites.

Table 11: Benign Cellular Changes Results

		ThinPrep		Conventional	
		N	%	N	%
Benign Cellular Changes	Infection	1392	20.6	1348	20.0
	Reactive Changes	412	6.1	471	7.0
	Total*	1592	23.6	1591	23.6

* Total includes some patients that may have had both an infection and reactive cellular change.

Tables 12, 13, and 14 show the specimen adequacy results for the ThinPrep method and conventional smear method for all of the study sites. Of the 7,360 total patients enrolled, 7,223 are included in this analysis. Cases with patient's age less than 18 years or patients with a hysterectomy were excluded from this analysis.

Two additional clinical studies were conducted to evaluate specimen adequacy results when samples were deposited directly into the PreservCyt vial, without first making a conventional Pap smear. This specimen collection technique is the intended use for the ThinPrep 2000 System. Tables 15 and 16 present the split sample and direct to vial results.

Table 12: Summary of Specimen Adequacy Results

Specimen Adequacy *Number of Patients: 7223*	ThinPrep N	ThinPrep %	Conventional N	Conventional %
Satisfactory	**5656**	**78.3**	**5101**	**70.6**
Satisfactory for Evaluation but Limited by:	**1431**	**19.8**	**2008**	**27.8**
Air-Drying Artifact	1	0.0	136	1.9
Thick Smear	9	0.1	65	0.9
Endocervical Component Absent	1140	15.8	681	9.4
Scant Squamous Epithelial Component	150	2.1	47	0.7
Obscuring Blood	55	0.8	339	4.7
Obscuring Inflammation	141	2.0	1008	14.0
No Clinical History	12	0.2	6	0.1
Cytolysis	19	0.3	119	1.6
Other	10	0.1	26	0.4
Unsatisfactory for Evaluation:	**136**	**1.9**	**114**	**1.6**
Air-Drying Artifact	0	0.0	13	0.2
Thick Smear	0	0.0	7	0.1
Endocervical Component Absent	25	0.3	11	0.2
Scant Squamous Epithelial Component	106	1.5	47	0.7
Obscuring Blood	23	0.3	58	0.8
Obscuring Inflammation	5	0.1	41	0.6
No Clinical History	0	0.0	0	0.0
Cytolysis	0	0.0	4	0.1
Other	31	0.4	9	0.1

Note: Some patients had more than one subcategory.

Table 13: Specimen Adequacy Results

		Conventional SAT	Conventional SBLB	Conventional UNSAT	Conventional TOTAL
Thin Prep	SAT	4316	1302	38	5656
	SBLB	722	665	44	1431
	UNSAT	63	41	32	136
	TOTAL	5101	2008	114	7223

SAT=Satisfactory, SBLB= Satisfactory But Limited By, UNSAT=Unsatisfactory

Table 14: Specimen Adequacy Results by Site

Site	Cases	ThinPrep SAT Cases	Convent. SAT Cases	ThinPrep SBLB Cases	Convent. SBLB Cases	ThinPrep UNSAT Cases	Convent. UNSAT Cases
S1	1,386	1092	1178	265	204	29	4
S2	1,668	1530	1477	130	178	8	13
S3	1,093	896	650	183	432	14	11
H1	1,046	760	660	266	375	20	11
H2	1,049	709	712	323	330	17	7
H3	981	669	424	264	489	48	68
All Sites	7,223	5656	5101	1431	2008	136	114

The Satisfactory But Limited By (SBLB) category can be broken down into many subcategories, one of which is the absence of Endocervical Component. Table 15 shows the Satisfactory But Limited By category "No ECC's" for ThinPrep and conventional slides.

Table 15: Specimen Adequacy Results by Site, SBLB Rates for no Endocervical Component

SBLB Due to No ECC's					
Site	Cases	ThinPrep SBLB-no ECC's	ThinPrep SBLB-no ECC's (%)	Conventional SBLB-no ECC's	Conventional SBLB-no ECC's (%)
S1	1,386	237	17.1%	162	11.7%
S2	1,668	104	6.2%	73	4.4%
S3	1,093	145	13.3%	84	7.7%
H1	1,046	229	21.9%	115	11.0%
H2	1,049	305	29.1%	150	14.3%
H3	981	120	12.2%	97	9.9%
All Sites	7,223	1140	15.8%	681	9.4%

For the results of the clinical study involving a split-sample protocol, there was a 6.4 percent difference between conventional and ThinPrep methods in detecting endocervical component. This is similar to previous studies using a split sample methodology.

For the intended use of the ThinPrep 2000 System, the broom-type cervical sampling device will be rinsed directly into a PreservCyt vial, rather than splitting the cellular sample. It was expected that this would result in an increase in the pick-up of endocervical cells and metaplastic cells. To verify this hypothesis, two studies were performed using the direct-to-vial method and are summarized in Table 16. Overall, no difference was found between ThinPrep and conventional methods in these two studies.

Table 16: Summary of Direct-to-Vial Studies

Study	Number of Evaluable Patients	SBLB due to No Endocervical Component	Comparable Conventional Pap Smear Percentage
Direct-to-Vial Feasibility	299	9.36%	9.43%[1]
Direct-to-Vial Clinical Study	484	4.96%	4.38%[2]

1. Direct-to-Vial Feasibility study compared to overall clinical investigation conventional Pap smear SBLB-No Endocervical Component rate.
2. Direct-to-Vial Clinical study compared to site S2 clinical investigation conventional Pap smear SBLB-No Endocervical Component rate.

CONCLUSIONS

The ThinPrep 2000 System is as effective as the conventional Pap smear in a variety of patient populations and may be used as a replacement for the conventional Pap smear method for the detection of atypical cells, cervical cancer, or its precursor lesions, as well as all other cytologic categories as defined by The Bethesda System.

The ThinPrep 2000 System is significantly more effective than the conventional Pap smear for the detection of Low Grade Squamous Intraepithelial (LSIL) and more severe lesions in a variety of patient populations.

Specimen quality with the ThinPrep 2000 System is significantly improved over that of conventional Pap smear preparation in a variety of patient populations.

MATERIALS REQUIRED

MATERIALS PROVIDED

The ThinPrep 2000 System consists of the following components:

- ThinPrep Processor Instrument (Model TP 2000)
- PreservCyt Solution vial
- TransCyt Filter for Gynecologic Applications
- Program Memory Card for Gynecologic Applications
- Power Cord
- 2 filter Caps
- 2 spare filter seal O-rings
- Waste bottle assembly - includes bottle, bottle cap, tubing set, fittings, waste filter
- ThinPrep Microscope slides

Additional items supplied:

- ThinPrep 2000 Operator's Manual
- 10 fixative vials
- Cervical collection device

MATERIALS REQUIRED BUT NOT PROVIDED

- Slide staining system and reagents
- Standard laboratory fixative
- Coverslips and mounting media

STORAGE

The storage condition for PreservCyt Solution *without* cytologic samples is up to one year from date of manufacture at 15° to 30°C

The storage limit for PreservCyt Solution *with* cytologic samples is 3 weeks at 4° to 37°C

BIBLIOGRAPHY

1. Kurman RJ, Solomon D. *The Bethesda System for Reporting Cervical/Vaginal Cytologic Diseases*, Springer-Verlag, New York 1994.

2. Jones HW. Impact of The Bethesda System, *Cancer* 77 pp. 1914-1918, 1995.

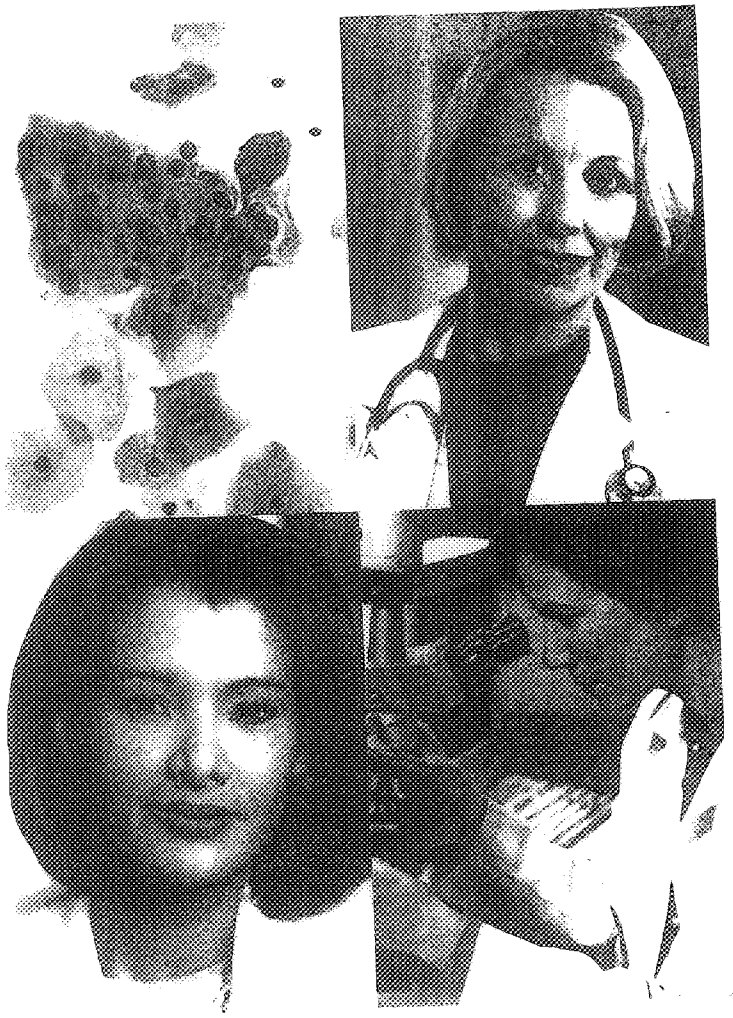
3. American Cancer Society. Cancer Facts and Figures, 1995.

TECHNICAL SERVICE AND PRODUCT INFORMATION

For technical service and assistance related to use of the ThinPrep 2000 System, contact Cytyc Corporation:

Telephone: 1-800-442-9892

Fax: 1-508-635-1033



ThinPrep® 2000 Operator's Manual

CYTYC

ThinPrep® 2000 System

FOR GYNECOLOGIC USE

Section 1 (clear tabs) describes the use of the ThinPrep Processor for Gynecologic applications. In addition, it contains all information regarding the installation, operation and maintenance of the ThinPrep 2000 System.

CYTYC
corporation

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FAX: (508) 635-1033

Part Number: 70090-001 Rev. D
For Use with Model: ThinPrep® 2000

Caution: Federal law restricts this device to sale by or on the order of a physician, or any other practitioner licensed by the law of the State in which the practitioner practices to use or order the use of the device and are trained and experienced in the use of the ThinPrep 2000 System.

Preparation of microscope slides using the ThinPrep 2000 System should be performed only by personnel who have been trained by Cytyc Corporation or by organizations or individuals designated by Cytyc Corporation.

Evaluation of microscope slides produced with the ThinPrep 2000 System should be performed only by cytotechnologists and pathologists who have been trained to evaluate ThinPrep prepared slides by Cytyc Corporation or by organizations or individuals designated by Cytyc Corporation.

Although this guide has been prepared with every precaution to ensure accuracy, Cytyc Corporation assumes no liability for any errors or omissions, nor for any damages resulting from the application or use of this information.

Cytyc, ThinPrep, ThinPrep Pap Test, TransCyt, CytoLyt, and PreservCyt are trademarks of Cytyc Corporation.

Changes or modifications to this unit not expressly approved by the party responsible for compliance could void the user's authority to operate the equipment.

This equipment has been tested and found to comply with the limits for a Class A digital device, pursuant to Park 15 of the FCC Rules. These limits are designed to provide reasonable protections against harmful interference when the equipment is operated in a commercial environment. This equipment generates, uses and can radiate radio frequency energy; and if not installed and used in accordance with the instruction manual, may cause interference to radio communications. Operation of this equipment in a residential area is likely to cause harmful interference, in which case the user will be required to correct the interference at his own expense.

Heirmit wird besheinig das ThinPrep Processor (Gerat, Typ, Bezeichnung ThinPrep® 2000) im Uebereinstimmung mit den Bestimmungen der Vfg 1046/1984 funk-entstort ist. Der Deutschen Bundespost wurde das Inverkehrbringen dieses Gerates angezeigt und die Berechtigung zur Ueberpruofung der Serie auf Einhaltung der Bestimmungen eingeraumt.

Translation: The ThinPrep Processor (Model ThinPrep® 2000) is shielded against radio interference in accordance with the provisions of Vfg 1046/1984. The German Postal Services have been advised that this device is being put on the market and that they have been given the right to inspect the series for compliance with the regulations.

Le present appareil numerique n'emet pas de bruits radioelectriques depassant les limites applicables aux appareils numeriques (de la class A) prescrites dans le Reglement sur le brouillage radioelectrique edicte par le ministere des Communications du Canada.

Translation: This digital apparatus does not exceed the (Class A) limits for radio noise emissions from digital apparatus set out in the Radio Interference Regulations of the Canadian Department of Communications.

Table of Contents

Chapter One

Introduction

Section A of this chapter provides an overview of the ThinPrep 2000 system for gynecologic applications. Section B describes the principles of operation of the ThinPrep 2000 System for gynecologic sample processing.

SECTION A

OVERVIEW OF THE THINPREP® PROCESSOR

INDICATION FOR USE

INTENDED USE

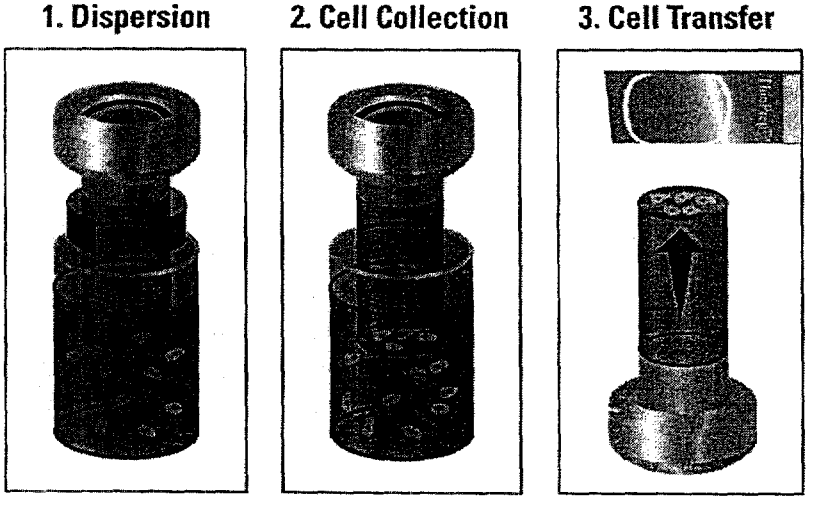
The ThinPrep® 2000 System is intended as a replacement for the conventional method of Pap smear preparation for use in screening for the presence of atypical cells, cervical cancer, or its precursor lesions (Low Grade Squamous Intraepithelial Lesions, High Grade Squamous Intraepithelial Lesions), as well as all other cytologic categories as defined by *The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses*[1].

SUMMARY AND EXPLANATION OF THE SYSTEM

The ThinPrep process begins with the patient's gynecologic sample being collected by the clinician using a broom-type cervical sampling device which, rather than being smeared on a microscope slide, is immersed and rinsed in a vial filled with PreservCyt Solution. The ThinPrep sample vial is then capped, labeled, and sent to a laboratory equipped with a ThinPrep 2000 Processor.

At the laboratory, the PreservCyt® sample vial is placed into a ThinPrep 2000 Processor and a gentle dispersion step breaks up blood, mucus, non-diagnostic debris, and thoroughly mixes the cell sample. The cells are then collected on a TransCyt® Filter specifically designed to collect diagnostic cells. The ThinPrep 2000 Processor constantly monitors the rate of flow through the TransCyt Filter during the collection process in order to prevent the cellular presentation from being too scant or too dense. A thin layer of cells is then transferred to a glass slide in a 20 mm-diameter circle, and the slide is automatically deposited into a fixative solution.

The ThinPrep Sample Preparation Process



(1) Dispersion
The TransCyt Filter rotates within the sample vial, creating currents in the fluid that are strong enough to separate debris and disperse mucus, but gentle enough to have no adverse effect on cell appearance.

(2) Cell Collection
A gentle vacuum is created within the TransCyt Filter, which collects cells on the exterior surface of the membrane. Cell collection is controlled by the ThinPrep 2000 Processor's software that monitors the rate of flow through the TransCyt Filter.

(3) Cell Transfer
After the cells are collected on the membrane, the TransCyt Filter is inverted and gently pressed against the ThinPrep Microscope Slide. Natural attraction and slight positive air pressure cause the cells to adhere to the ThinPrep Microscope Slide resulting in an even distribution of cells in a defined circular area.

As with conventional Pap smears, slides prepared with the ThinPrep 2000 System are examined in the context of the patient's clinical history and information provided by other diagnostic procedures such as colposcopy, biopsy, and human papillomavirus (HPV) testing, to determine patient management.

The ThinPrep 2000 Processor is also marketed for non-gynecologic applications. This Operator's Manual is specific for the gynecologic use of the device.

LIMITATIONS

- Gynecologic samples collected for preparation using the ThinPrep 2000 System should be collected using a broom type collection device.
- Preparation of microscope slides using ThinPrep 2000 System should be performed only by personnel who have been trained by Cytyc Corporation or by organizations or individuals designated by Cytyc Corporation.
- Evaluation of microscope slides produced with the ThinPrep 2000 System should be performed only by cytotechnologists and pathologists who have been trained to evaluate ThinPrep prepared slides by Cytyc Corporation or by organizations or individuals designated by Cytyc Corporation. See Chapter 9 for a summary of the ThinPrep Processor training program.
- Supplies used in the ThinPrep 2000 System are those designed and supplied by Cytyc Corporation specifically for the ThinPrep 2000 System. These include PreservCyt Solution vials, TransCyt Filters, and ThinPrep Microscope Slides. These supplies are required for proper performance of the system and cannot be substituted. Product performance will be compromised if other supplies are used. After use, supplies should be disposed of in accordance with local, state, and federal regulations.
- A TransCyt Filter must be used only once and cannot be reused.

WARNINGS

- PreservCyt Solution contains methanol which is poisonous and may be fatal or cause blindness if swallowed. Methanol vapor may be harmful. PreservCyt is flammable; keep away from fire, heat, sparks, and flame. Other solutions must not be substituted for PreservCyt solution. PreservCyt Solution should be stored and disposed of in accordance with local, state, and federal regulations.

PRECAUTIONS

- This equipment generates, uses and can radiate radio frequency energy, and if not installed and used in accordance with the Operator's Manual, may cause interference to radio communications. Operation of this equipment in a residential area is likely to cause harmful interference, in which case the user will be required to correct the interference at his/her own expense.
- The storage limit for cells in PreservCyt is 3 weeks at 4° to 37°C
- PreservCyt Solution is anti-microbial. PreservCyt Solution has been shown to cause greater than 99.999 percent inactivation within 15 minutes for the following microbes: *Candida albicans, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Mycobacterium tuberculosis.* As with all laboratory procedures, universal precautions should be followed.

PERFORMANCE CHARACTERISTICS: REPORT OF CLINICAL STUDY

A prospective multi-center clinical study was conducted to evaluate the performance of the ThinPrep 2000 System in direct comparison to the conventional Pap smear. The objective of the ThinPrep clinical study was to demonstrate that gynecologic specimens prepared using the ThinPrep 2000 System were at least as effective as conventional Pap smears for the detection of atypical cells and cervical cancer or its precursor lesions in a variety of patient populations. In addition, an assessment of specimen adequacy was performed.

The initial clinical study protocol was a blinded, split sample, matched pair study, for which a conventional Pap smear was prepared first, and the remainder of the sample (the portion that normally would have been discarded) was immersed and rinsed into a vial of PreservCyt Solution. At the laboratory, the PreservCyt sample vial was placed into a ThinPrep 2000 Processor and a slide was then prepared from the patient's sample. ThinPrep and conventional Pap smear slides were examined and diagnosed independently. Reporting forms containing patient history as well as a checklist of all possible categories of The Bethesda System were used to record the results of the screening. A single independent pathologist reviewed all discrepant and positive slides from all sites in a blinded fashion to provide a further objective review of the results.

LABORATORY AND PATIENT CHARACTERISTICS

Cytology laboratories at three screening centers (designated as S1, S2, and S3) and three hospital centers (designated as H1, H2, and H3) participated in the clinical study. The screening centers in the study serve patient populations (screening populations) with rates of abnormality (Low Grade Squamous Intraepithelial Lesion [LSIL] and more severe lesions) similar to the United States average of less than 5%.[2] The hospital centers in the study serve a high risk referral patient population (hospital populations) characterized by high rates (>10%) of cervical abnormality.

Data on race demographics was obtained for 70% of the patients that participated in the study. The study population consisted of the following race groups: Caucasian (41.2%), Asian (2.3%), Hispanic (9.7%), African American (15.2%), Native American (1.0%) and other groups (0.6%). Table 1 describes the laboratories and the patient populations.

Table 1: Site Characteristics

Laboratory Characteristics			Clinical Study Demographics				
Site	Type of Patient Population	Laboratory Volume – Smears per Year	Cases	Patient Age Range	Post-Meno-pausal	Previous Abnormal Pap Smear	Conventional Prevalence LSIL+
S1	Screening	300,000	1,386	18.0 - 84.0	10.6%	8.8%	2.3%
S2	Screening	100,000	1,668	18.0 - 60.6	0.3%	10.7%	2.9%
S3	Screening	96,000	1,093	18.0 - 48.8	0.0%	7.1%	3.8%
H1	Hospital	35,000	1,046	18.1 - 89.1	8.1%	40.4%	9.9%
H2	Hospital	40,000	1,049	18.1 - 84.4	2.1%	18.2%	12.9%
H3	Hospital	37,000	981	18.2 - 78.8	11.1%	38.2%	24.2%

CLINICAL STUDY RESULTS

The diagnostic categories of The Bethesda System were used as the basis of the comparison between conventional and ThinPrep findings from the clinical study. The diagnostic classification data and statistical analyses for all clinical sites are presented in Tables 2 through 11. Cases with incorrect paperwork, patient's age less than 18 years, cytologically unsatisfactory slides, or patients with a hysterectomy were excluded from this analysis. Few cases of cervical cancer (0.02%[3]) were represented in the clinical study, as is typical in the United States patient population.

Table 2: Diagnostic Classification Table, All Categories

		Conventional							
		NEG	ASCUS	AGUS	LSIL	HSIL	SQCA	GLCA	TOTAL
Thin-Prep	Neg	5022	295	3	60	11	0	0	5593
	ASCUS	318	122	2	45	7	0	0	497
	AGUS	13	2	3	0	1	0	1	20
	LSIL	114	84	0	227	44	0	0	469
	HSIL	11	15	0	35	104	2	0	167
	SQ CA	0	0	0	0	0	1	0	1
	GL CA	0	0	0	0	0	0	0	0
	TOTAL	5680	521	8	367	167	3	1	6747

Abbreviations for Diagnoses: NEG = Normal or negative, ASCUS = Atypical Squamous Cells of Undetermined Significance, AGUS = Atypical Glandular Cells of Undetermined Significance, LSIL = Low-grade Squamous Intraepithelial Lesion, HSIL = High-grade Squamous Intraepithelial Lesion, SQ CA = Squamous Cell Carcinoma, GL CA = Glandular Cell Adenocarcinoma

Table 3: Three Category Diagnostic Classification Table

		Conventional			
		NEG	ASCUS/ AGUS	LSIL+	TOTAL
Thin-Prep	NEG	5224	298	71	5593
	ASCUS/AGUS	331	116	54	517
	LSIL+	125	99	413	637
	TOTAL	5680	529	538	6747

Table 4: Two Category Diagnostic Classification Table, LSIL and More Severe Diagnoses

		Conventional		
		NEG/ASCUS/ AGUS	LSIL+	TOTAL
Thin-Prep	NEG/ASCUS/AGUS	6085	125	6110
	LSIL+	224	413	637
	TOTAL	6209	538	6747

Table 5: Two Category Diagnostic Classification Table, ASCUS/AGUS and More Severe Diagnoses

		Conventional		
		NEG	ASCUS/AGUS+	TOTAL
Thin-Prep	NEG	5224	369	5593
	ASCUS/AGUS+	456	698	1154
	TOTAL	5680	1067	6747

The diagnostic data analysis from the sites is summarized in Tables 6 and 7. When the p-value is significant ($p < 0.05$), the method favored is indicated in the tables.

Table 6: Results by Site, LSIL and More Severe Lesions

Site	Cases	ThinPrep LSIL+	Convent LSIL+	Increased Detection*	p-Value	Method Favored
S1	1,336	46	31	48%	0.027	ThinPrep
S2	1,563	78	45	73%	<0.001	ThinPrep
S3	1,058	67	40	68%	<0.001	ThinPrep
H1	971	125	96	30%	<0.001	ThinPrep
H2	1,010	111	130	(15%)	0.135	Neither
H3	809	210	196	7%	0.374	Neither

*Increased detection = $\frac{\text{ThinPrepLSIL+ - Conventional LSIL+}}{\text{Conventional LSIL+}} \times 100\%$

For LSIL and more severe lesions, the diagnostic comparison statistically favored the ThinPrep method at four sites and was statistically equivalent at two sites.

Table 7: Results by Site, ASCUS/AGUS and More Severe Lesions

Site	Cases	ThinPrep ASCUS+	Convent. ASCUS+	Increased Detection*	p-Value	Method Favored
S1	1,336	117	93	26%	0.067	Neither
S2	1,563	124	80	55%	<0.001	ThinPrep
S3	1,058	123	81	52%	<0.001	ThinPrep
H1	971	204	173	18%	0.007	ThinPrep
H2	1,010	259	282	(8%)	0.360	Neither
H3	809	327	359	(9%)	0.102	Neither

*Increased detection = $\frac{\text{ThinPrepLSIL+ - Conventional LSIL+}}{\text{Conventional LSIL+}} \times 100\%$

For ASCUS/AGUS and more severe lesions, the diagnostic comparison statistically favored the ThinPrep method at three sites and was statistically equivalent at three sites.

One pathologist served as an independent reviewer for the six clinical sites, receiving both slides from cases where the two methods were either abnormal or discrepant. Since a true reference cannot be determined in such studies and therefore true sensitivity cannot be calculated, the use of an expert cytologic review provides an alternative to histologic confirmation by biopsy or human papillomavirus (HPV) testing as a means for determining the reference diagnosis.

The reference diagnosis was the more severe diagnosis from either of the ThinPrep or conventional Pap slides as determined by the independent pathologist. The number of slides diagnosed as abnormal at each site, compared to the reference diagnosis of the independent pathologist, provides the proportion of LSIL or more severe lesions (Table 8) and the proportion of ASCUS/AGUS or more severe lesions (Table 9). The statistical analysis allows a comparison of the two methods and a determination of which method is favored when using the independent pathologist for expert cytologic review as the adjudicator of the final diagnosis.

Table 8: Independent Pathologist Results by Site, LSIL and More Severe Lesions

Site	Cases	ThinPrep Positive	Conventional Positive	p-Value	Method Favored
S1	50	33	25	0.170	Neither
S2	65	48	33	0.042	ThinPrep
S3	77	54	33	<0.001	ThinPrep
H1	116	102	81	<0.001	ThinPrep
H2	115	86	90	0.876	Neither
H3	126	120	112	0.170	Neither

For LSIL and more severe lesions, the diagnostic comparison statistically favored the ThinPrep method at three sites and was statistically equivalent at three sites.

Table 9: Independent Pathologist Results by Site, ASCUS/AGUS and More Severe Lesions

Site	Cases	ThinPrep Positive	Conventional Positive	p-Value	Method Favored
S1	92	72	68	0.900	Neither
S2	101	85	59	0.005	ThinPrep
S3	109	95	65	<0.001	ThinPrep
H1	170	155	143	0.237	Neither
H2	171	143	154	0.330	Neither
H3	204	190	191	1.000	Neither

For ASCUS/AGUS and more severe lesions, the diagnostic comparison statistically favored the ThinPrep method at two sites and was statistically equivalent at four sites.

Table 10 below shows the summary for all sites of the descriptive diagnosis for all Bethesda System categories.

Table 10: Summary of Descriptive Diagnosis

Descriptive Diagnosis *Number of Patients: 6747*	ThinPrep		Conventional	
	N	%	N	%
Benign Cellular Changes:	**1592**	**23.6**	**1591**	**23.6**
Infection:				
Trichomonas Vaginalis	136	2.0	185	2.7
Candida spp.	406	6.0	259	3.8
Coccobacilli	690	10.2	608	9.0
Actinomyces spp.	2	0.0	3	0.0
Herpes	3	0.0	8	0.1
Other	155	2.3	285	4.2
Reactive Cellular Changes Associated with:				
Inflammation	353	5.2	385	5.7
Atrophic Vaginitis	32	0.5	48	0.7
Radiation	2	0.0	1	0.0
Other	25	0.4	37	0.5
Epithelial Cell Abnormalities:	**1159**	**17.2**	**1077**	**16.0**
Squamous Cell:				
ASCUS	501	7.4	521	7.7
favor reactive	128	1.9	131	1.9
favor neoplastic	161	2.4	140	2.1
undetermined	213	3.2	250	3.7
LSIL	469	7.0	367	5.4
HSIL	167	2.5	167	2.5
Carcinoma	1	0.0	3	0.0
Glandular Cell:				
Benign Endometrial cells in Postmenopausal Women	7	0.1	10	0.1
Atypical Glandular Cells (AGUS)	21	0.3	9	0.1
favor reactive	9	0.1	4	0.1
favor neoplastic	0	0.0	3	0.0
undetermined	12	0.2	2	0.0
Endocervical Adenocarcinoma	0	0.0	1	0.0

Note: Some patients had more than one diagnostic subcategory.

Table 11 shows the rates of detection for infection, reactive changes, and the total benign cellular changes for both the ThinPrep and conventional methods at all sites.

Table 11: Benign Cellular Changes Results

		ThinPrep		Conventional	
		N	%	N	%
Benign Cellular Changes	**Infection**	1392	20.6	1348	20.0
	Reactive Changes	412	6.1	471	7.0
	Total*	1592	23.6	1591	23.6

* Total includes some patients that may have had both an infection and reactive cellular change.

Tables 12, 13 and 14 show the specimen adequacy results for the ThinPrep method and conventional smear method for all of the study sites. Of the 7,360 total patients enrolled, 7,223 are included in this analysis. Cases with patient's age less than 18 years or patients with a hysterectomy were excluded from this analysis.

Two additional clinical studies were conducted to evaluate specimen adequacy results when samples were deposited directly into the PreservCyt vial, without first making a conventional Pap smear. This specimen collection technique is the intended use for the ThinPrep 2000 System. Tables 15 and 16 present the split sample and direct to vial results.

Table 12: Summary of Specimen Adequacy Results

Specimen Adequacy *Number of Patients: 7223*	ThinPrep		Conventional	
	N	%	N	%
Satisfactory	**5656**	**78.3**	**5101**	**70.6**
Satisfactory for Evaluation but Limited by:	**1431**	**19.8**	**2008**	**27.8**
Air-Drying Artifact	1	0.0	136	1.9
Thick Smear	9	0.1	65	0.9
Endocervical Component Absent	1140	15.8	681	9.4
Scant Squamous Epithelial Component	150	2.1	47	0.7
Obscuring Blood	55	0.8	339	4.7
Obscuring Inflammation	141	2.0	1008	14.0
No Clinical History	12	0.2	6	0.1
Cytolysis	19	0.3	119	1.6
Other	10	0.1	26	0.4
Unsatisfactory for Evaluation:	**136**	**1.9**	**114**	**1.6**
Air-Drying Artifact	0	0.0	13	0.2
Thick Smear	0	0.0	7	0.1
Endocervical Component Absent	25	0.3	11	0.2
Scant Squamous Epithelial Component	106	1.5	47	0.7
Obscuring Blood	23	0.3	58	0.8
Obscuring Inflammation	5	0.1	41	0.6
No Clinical History	0	0.0	0	0.0
Cytolysis	0	0.0	4	0.1
Other	31	0.4	9	0.1

Note: Some patients had more than one subcategory.

Table 13: Specimen Adequacy Results

		Conventional			
		SAT	SBLB	UNSAT	TOTAL
Thin-Prep	SAT	4316	1302	38	5656
	SBLB	722	665	44	1431
	UNSAT	63	41	32	136
	TOTAL	5101	2008	114	7223

SAT=Satisfactory, SBLB-Satisfactory But Limited By, UNSAT=Unsatisfactory

Table 14: Specimen Adequacy Results by Site

Site	Cases	ThinPrep SAT Cases	Convent. SAT Cases	ThinPrep SBLB Cases	Convent. SBLB Cases	ThinPrep UNSAT Cases	Convent. UNSAT Cases
S1	1,386	1092	1178	265	204	29	4
S2	1,668	1530	1477	130	178	8	13
S3	1,093	896	650	183	432	14	11
H1	1,046	760	660	266	375	20	11
H2	1,049	709	712	323	330	17	7
H3	981	669	424	264	489	48	68
All Sites	7,223	5656	5101	1431	2008	136	114

The Satisfactory But Limited By (SBLB) category can be broken down into many subcategories, one of which is the absence of Endocervical Component. Table 15 shows the Satisfactory But Limited By category "No ECC's" for ThinPrep and conventional slides.

Table 15: Specimen Adequacy Results by Site, SBLB Rates for no Endocervical Component.

SBLB Due to No ECC's					
Site	Cases	ThinPrep SBLB -no ECC's	ThinPrep SBLB -no ECC's (%)	Conventional SBLB -no ECC's	Conventional SBLB -no ECC's (%)
S1	1,386	237	17.1%	162	11.7%
S2	1,668	104	6.2%	73	4.4%
S3	1,093	145	13.3%	84	7.7%
H1	1,046	229	21.9%	115	11.0%
H2	1,049	305	29.1%	150	14.3%
H3	981	120	12.2%	97	9.9%
All Sites	7,223	1140	15.8%	681	9.4%

For the results of the clinical study involving a split-sample protocol, there was a 6.4 percent difference between conventional and ThinPrep methods in detecting endocervical component. This is similar to previous studies using a split sample methodology. For the intended use of the ThinPrep 2000 System, the broom-type cervical sampling

device will be rinsed directly into a PreservCyt vial, rather than splitting the cellular sample. It was expected that this would result in an increase in the pick-up of endocervical cells and metaplastic cells. To verify this hypothesis, two studies were performed using the direct-to-vial method and are summarized in Table 16. Overall, no difference was found between ThinPrep and conventional methods in these two studies.

Table 16: Summary of Direct-to-Vial Studies

Study	Number of Evaluable Patients	SBLB due to No Endocervical Component	Comparable Conventional Pap Smear Percentage
Direct-to-Vial Feasibility	299	9.36%	9.43%[1]
Direct-to-Vial Clinical Study	484	4.96%	4.38%[2]

1. Direct-to-Vial Feasibility study compared to overall clinical investigation conventional Pap smear SBLB-No Endocervical Component rate.
2. Direct-to-Vial Clinical study compared to site S2 clinical investigation conventional Pap smear SBLB-No Endocervical Component rate.

CONCLUSIONS

The ThinPrep 2000 System is as effective as the conventional Pap smear in a variety of patient populations and may be used as a replacement for the conventional Pap smear method for the detection of atypical cells, cervical cancer, or its precursor lesions, as well as all other cytologic categories as defined by The Bethesda System.

The ThinPrep 2000 System is significantly more effective than the conventional Pap smear for the detection of Low Grade Squamous Intraepithelial (LSIL) and more severe lesions in a variety of patient populations.

Specimen quality with the ThinPrep 2000 System is significantly improved over that of conventional Pap smear preparation in a variety of patient populations.

MATERIALS REQUIRED

MATERIALS PROVIDED

The ThinPrep 2000 System consists of the following components:

- ThinPrep Processor Instrument (Model: ThinPrep 2000)
- Program Memory Card
- Power Cord
- 2 filter Caps
- 2 spare filter seal O-rings
- Waste bottle assembly – includes bottle, bottle cap, tubing set, fittings, waste filter
- 10 fixative vials
- ThinPrep 2000 Operator's Manual

Items available as part of the ThinPrep Pap Test:

- PreservCyt Solution Vial
- Gyn TransCyt Filter (Clear) for Gynecologic Applications
- ThinPrep Microscope Slides

Item available separately from the ThinPrep Pap Test:

- Cervical Collection Device

MATERIALS REQUIRED BUT NOT PROVIDED

- Slide staining system and reagents
- Standard laboratory fixative
- Coverslips and mounting media

STORAGE

The storage condition for PreservCyt Solution *without* cytologic samples is up to one year from date of manufacture at 15° to 30°C

The storage limit for PreservCyt Solution *with* cytologic samples is 3 weeks at 4° to 37°C

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2. Jones HW. Impact of The Bethesda System, *Cancer* 77 pp. 1914-1918, 1995
3. American Cancer Society. Cancer Facts and Figures – 1995.

SECTION B

PRINCIPLES OF OPERATION

The ThinPrep Processor makes use of mechanical, pneumatic, and fluidic principles for cell dispersion, collection, and transfer. A rotary drive mechanism gently disperses samples. A pneumatic/fluidic system, controlled by a microprocessor, monitors cell collection. Electrochemical principles, the pneumatic and fluidic systems, the natural binding qualities of cells, and the qualities of the Cytyc TransCyt Filter are responsible for cell transfer.

Each ThinPrep Processor slide preparation processing sequence is optimized for the biological characteristics of the various cytological specimens.

The ThinPrep Processor slide preparation process can be divided into the following phases:

- Sample preparation/Instrument loading
- Start of cycle
- Fluid level detection
- Dispersion
- Filter wetting
- Cell collection
- Waste clearing
- Bubble point
- Cell transfer
- Slide ejection
- Completion of cycle

The following sections describe the principles of each of these phases in detail.

Sample Preparation/Instrument Loading

Before the ThinPrep Processor can process samples, the samples must be placed into PreservCyt Solution. Gynecologic samples must be prepared according to the protocols described in Chapter 8, *Gynecologic Sample Preparation.* Once the cells are added to the PreservCyt Solution vial by the appropriate method, the instrument can process the sample vial.

In preparation for sample processing, the operator loads four essential items into the instrument: a PreservCyt Sample vial, a TransCyt Filter attached to the filter cap, a ThinPrep Slide and a fixative bath containing a standard laboratory fixative. The processes of loading and operating the instrument are explained in Chapter 3, *Operating Instructions.*

Start of Cycle

When the operator initiates a sequence, the ThinPrep Processor verifies installation of disposables, motor positions, and the positive and negative pressures in the pressure reservoirs. After this the instrument processes the slide using the selected sequence.

Fluid Level Detection

The cap seal lowers to seal the filter assembly and the sample vial is raised towards the filter membrane. The sample vial stops when the filter membrane makes contact with the surface of fluid. If the fluid level is satisfactory, the instrument will continue the slide preparation process. An error message and audible alarm indicate an unsatisfactory fluid level.

Dispersion

The cap seal lifts and the dispersion system rotates the TransCyt Filter assembly within the cell suspension, creating shear forces in the fluid that are strong enough to separate randomly joined material and disperse mucus, and are not known to have an adverse effect on the cellular architecture or on adhesive forces joining diagnostically relevant groups of cells.

Filter Wetting

The head seal lowers to seal the filter assembly. Negative pressure is briefly applied, drawing a small amount of fluid through the TransCyt Filter to wet it. Following wetting, the system gently blows out the liquid in the TransCyt Filter. This clears any cellular material from the filter surface.

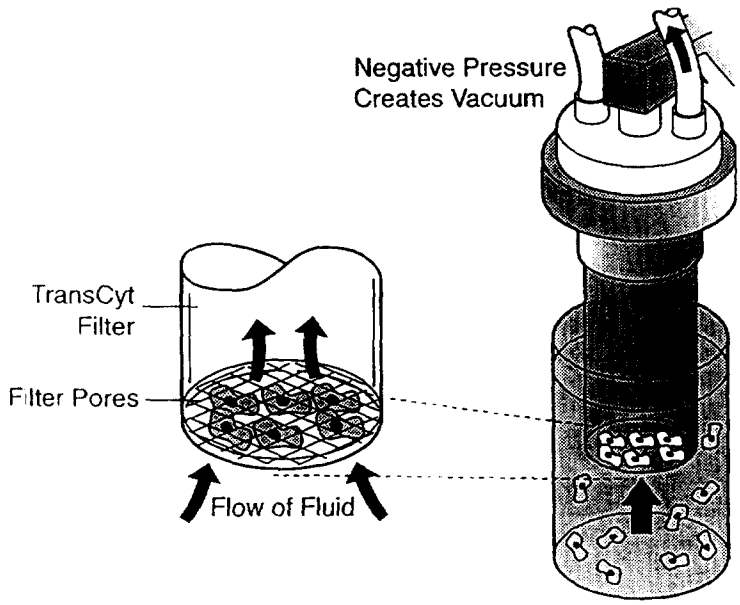
Cell Collection

The filter membrane is biologically neutral and is mounted at one end of the TransCyt Filter cylinder. The membrane is a flat, smooth, porous surface that collects the cellular material on one plane.

The pneumatic system applies negative pressure to the filter in a series of pulses. These negative pressure pulses (sips) draw PreservCyt Solution through the filter membrane and collect suspended cellular material onto the outer membrane surface.

The collection process ceases when a target filter coverage, predetermined by the processor sequence, is attained. Cell collection is controlled by an embedded microprocessor that monitors the pressure in the TransCyt Filter cylinder. After collection, the cells sit on a single plane over the pores, ready for transfer to the slide. Figure 1-3 illustrates cell collection.

Figure 1-3 Cell Collection.



Waste Clearing

When collection ends, the TransCyt Filter is withdrawn from the sample vial and the filtrate is aspirated into the waste bottle as the filter is inverted. The collected cells remain on the TransCyt Filter due to the negative holding pressure.

Bubble Point

Bubble point removes excess fluid from the filter membrane prior to transferring cells onto the slide to enhance cell adhesion to the slide.

Bubble point is performed after all of the fluid is evacuated. This is evident by the bubbling activity on the inside of the filter membrane. Cells do not air-dry during bubble point.

Cell Transfer

When bubble point is complete, the slide handler moves the slide into contact with the inverted TransCyt Filter.

The natural adhesion properties of cells and the electrochemical charge of the glass slide are responsible for the transfer of cells from the filter membrane to the slide. The cells have a higher affinity for the glass slide than for the membrane; slight positive air pressure behind the filter membrane enhances cell transfer.

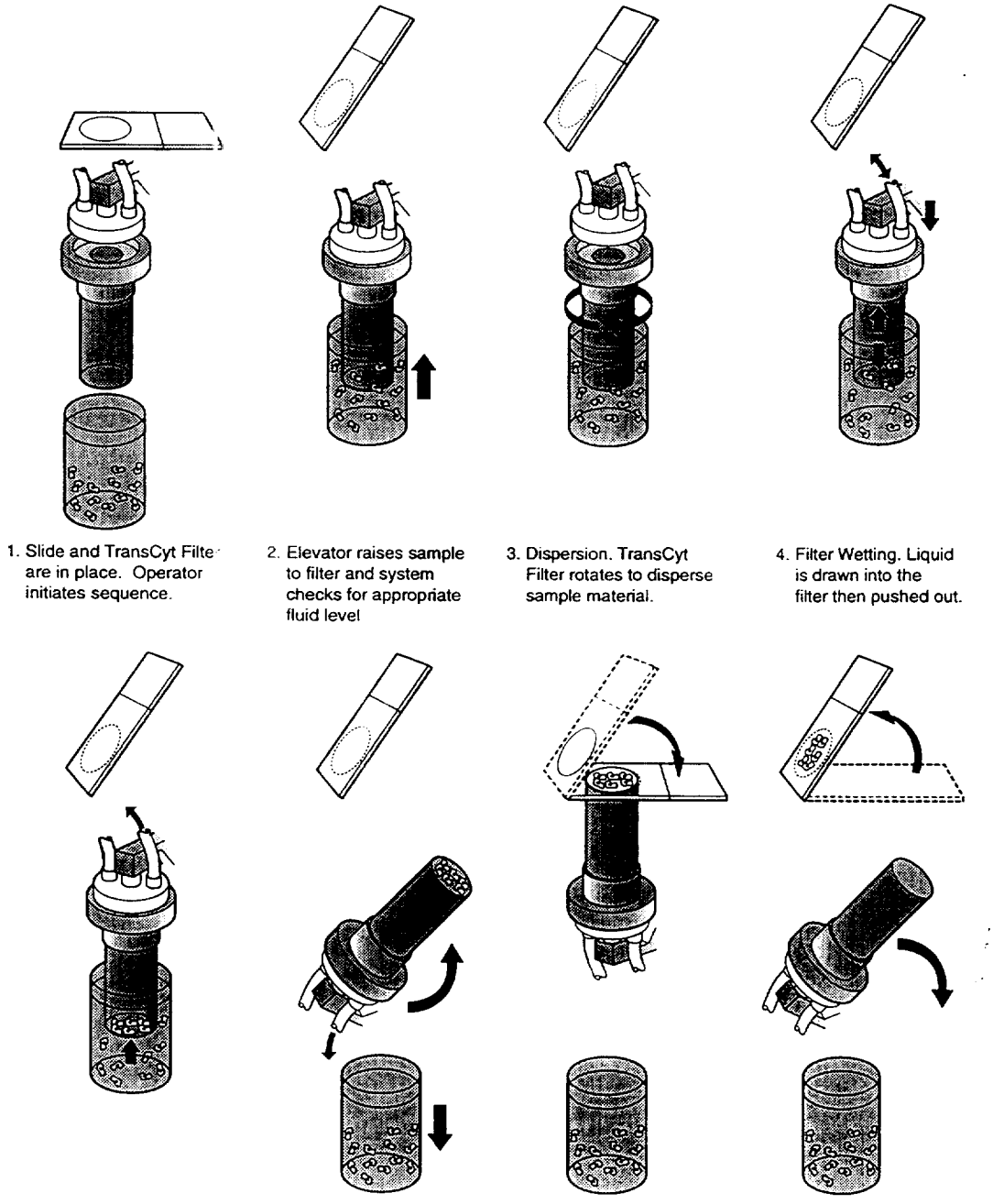
Slide Ejection

Once cell transfer is complete, the slide is removed from contact with the filter and automatically ejected into the fixative bath vial.

Cycle Completion

All the motorized mechanisms return to their initial positions and the display returns to the Main Menu. If the system detects an error during the process, a message will be displayed and an audible alarm will sound.

Figure 1-4 Overview of processing.



1. Slide and TransCyt Filter are in place. Operator initiates sequence.
2. Elevator raises sample to filter and system checks for appropriate fluid level
3. Dispersion. TransCyt Filter rotates to disperse sample material.
4. Filter Wetting. Liquid is drawn into the filter then pushed out.
5. Cell Collection. Sample is drawn onto TransCyt Filter in a controlled manner.
6. Waste Clearing. Filter is inverted, waste is cleared to waste bottle and Sample vial is lowered
7. Cell Transfer. Slide holder contacts filter. Cells are transferred to slide
8. Slide Ejection. Slide is deposited into fixative bath. Filter returns to starting point.

Chapter Two

Installation And Specifications

SECTION A

INTRODUCTION

This section provides information for unpacking and installing your ThinPrep Processor. Please ***completely*** follow the installation procedure, step by step, to ensure proper installation and system operation.

Before proceeding with the installation of the ThinPrep Processor, compare the contents of the shipping container with the checklist below. If any items are missing or damaged, contact Cytyc Customer Service at 1-800-442-9892 or (508) 263-8000.

Checklist for contents of shipping container and accessory kit.

- ✔ ThinPrep® 2000
- ✔ ThinPrep® 2000 Operator's Manual
- ✔ Program Memory Card
- ✔ Power cord, 6 feet
- ✔ 2 filter caps
- ✔ 2 spare filter seal O-rings
- ✔ Waste bottle assembly – includes bottle, bottle cap, tubing set, fittings, waste filter
- ✔ 10 fixative vials
- ✔ #1 Tip (small) Phillips head screwdriver
- ✔ #2 Tip (large) Phillips head screwdriver with string attached
- ✔ Cutter for tie wraps
- ✔ O-ring lubricant grease
- ✔ Replacement tubing for evacuation system
- ✔ Waste bottle cap for bottle transport
- ✔ Sealed cylinder for testing

Turning the power on before instructed to do so can damage the instrument and invalidate your warranty.

SECTION B

THINPREP PROCESSOR SPECIFICATIONS

	ThinPrep Processor	Waste Bottle
Dimensions	W = 18" / 46 cm H = 19.5" / 50 cm D = 15" / 38 cm	W = 6" / 15 cm H = 17" / 43 cm D = 6" / 15 cm
Weight	41 lbs (approx.)	
Clearance	Front = 0" / 0cm Rear = 3" / 8cm Side(ea) = 3" / 8cm Top = 3" / 8cm	Front = 1" / 3cm Rear = 1" / 3cm Side(ea) = 1" / 3cm Top = 0" / 0cm
Operating Temperature	15 – 32°C 59 – 90°F	
Operating Humidity	20% – 90% RH non-condensing	
Electrical Voltage	100/120 VAC at 2 amps 220/240 VAC at 1 amp	
Frequency	47– 63 Hz	
Power	Maximum 200 watts	

SECTION C

LOCATION SELECTION INFORMATION

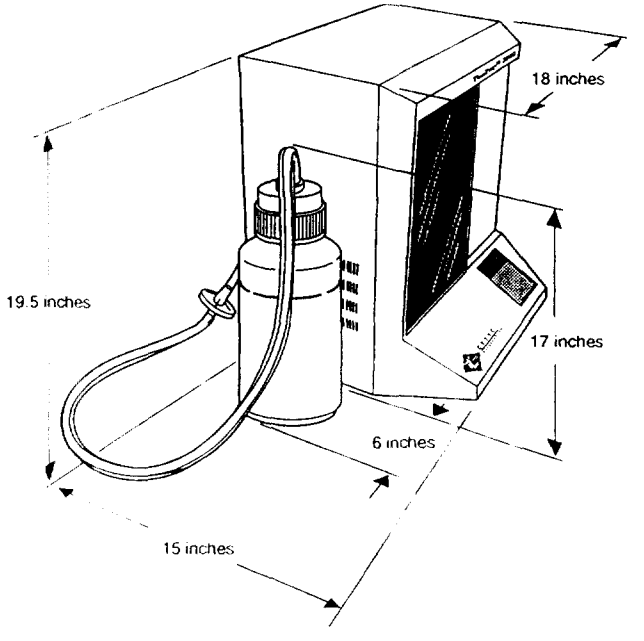
Locate the ThinPrep Processor near a 3-prong grounded power outlet that is free of voltage fluctuations and power surges. As with most laboratory equipment, it may be necessary to install a line voltage stabilizer to eliminate power fluctuations and minimize interference from other systems.

During operation the ThinPrep Processor is sensitive to vibrations. It should be placed on a sturdy bench away from centrifuges, vortexors, or any other equipment that may cause vibrations. If the location of the ThinPrep Processor must be in proximity to one of these devices, the ThinPrep Processor should not be operating at the same time as any of these other devices.

Allowing for adequate clearances, the following space is required for the ThinPrep Processor: H = 22.5" W = 24" D = 18".

The waste bottle may be placed either on the bench with the processor or below the processor. The waste bottle will occupy an area approximately a 6 inch square by 17 inches high.

Figure 2-1 ThinPrep Processor system dimensions



SECTION D

INTERNAL PACKAGING REMOVAL

The inside mechanism of the ThinPrep Processor is secured for shipment in two areas. A bracket and rubber strip secure the rotating plate in a vertical position, and two tie wraps with a foam block secure the slide handler. These internal securements must be removed before operating the instrument. Do not turn on the power of the processor until instructed to do so.

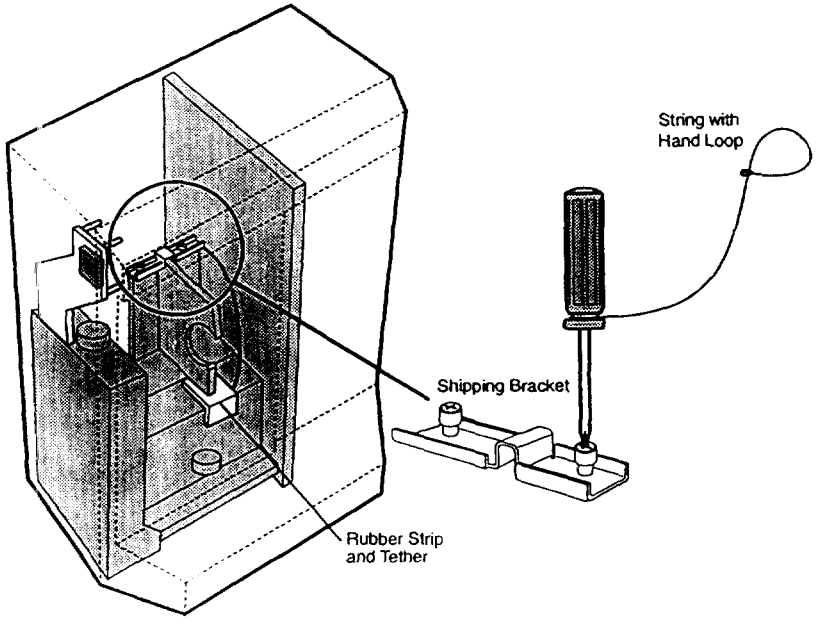
Turning the power on before instructed to do so can damage the instrument and invalidate your warranty.

WARNING: Be extremely careful not to drop the screwdriver during this procedure because it may be difficult to retrieve. Use the screwdriver's safety line for insurance.

Rotating Plate Packaging Removal:

1. Open the door of the ThinPrep Processor by sliding it to the right.
2. Slip your hand through the loop at the end of the string attached to the #2 tip (large) Phillips head screwdriver (provided) and loosen the two screws on the top of the bracket as shown in figure 2-2.
3. Continue to loosen the screws by hand until the bracket is free. The screws are captured in the bracket and cannot be completely removed.

Figure 2-2 Removing the rotating plate packaging



4. Remove the bracket by lifting it straight up and then withdraw it from the instrument. The bracket is tethered to a rubber strip under the end of the rotating plate. Do not cut this tether joining the two parts. Refer to figure 2-2.

5 Remove the rubber strip by grasping the end of the strip and pulling it straight out of the instrument.

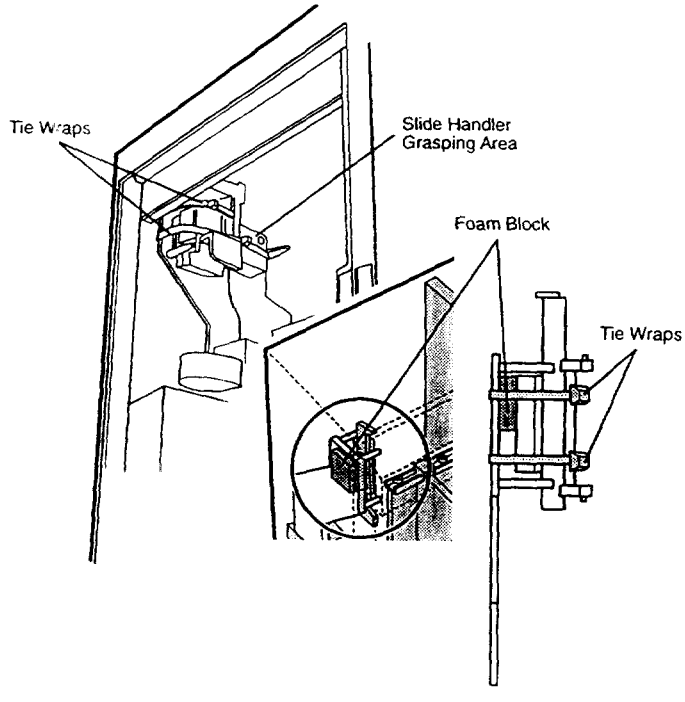
6 The rotating plate can be turned clockwise into a horizontal position.

7 Save the screwdriver, bracket and rubber strip for instrument packaging. **Note:** The #1 tip (small) Phillips head screwdriver will be used for periodic instrument maintenance.

Slide Handler Packaging Removal:

1. Locate the ***two*** tie wraps securing the slide handler. The tie wraps are located around the slide handler in the upper left-hand corner of the instrument. Refer to figure 2-3.

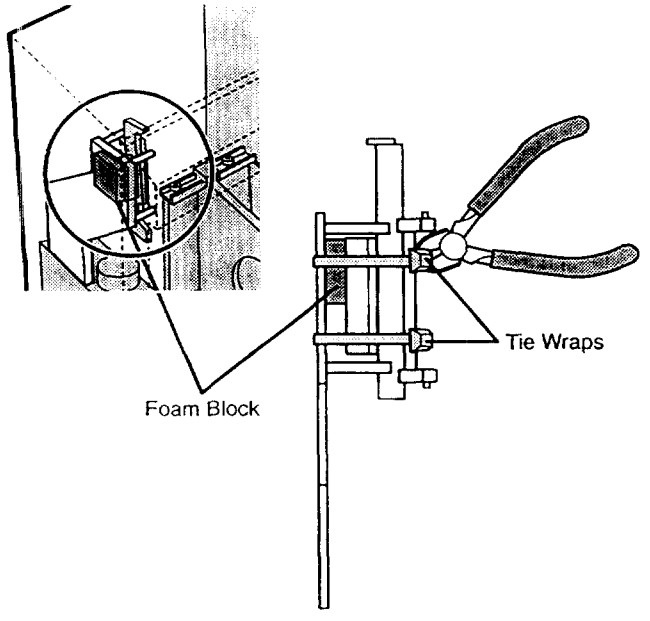
Figure 2-3 Locating the two tie wraps



2. Using the cutters provided, carefully cut the two tie wraps from the slide handler. Refer to figure 2-4.

Use extreme care and only cut the two tie wraps around the slide handler.

Figure 2-4 Removing the slide handler packaging



3. Carefully remove the cut tie wraps from the slide handler. It may be necessary to rotate the slide handler to a horizontal position to gain access to the cut tie wraps. To rotate the slide handler, grasp the slide handler in the area which is indicated on figure 2-3.
4. Carefully remove the foam block that was between the slide handler and the four horizontal ejector pins. The foam block may still be between the four ejector pins in the upper left-hand corner of the unit.
5. Close the door by sliding it to the left.
6. Save the foam block for instrument packaging.

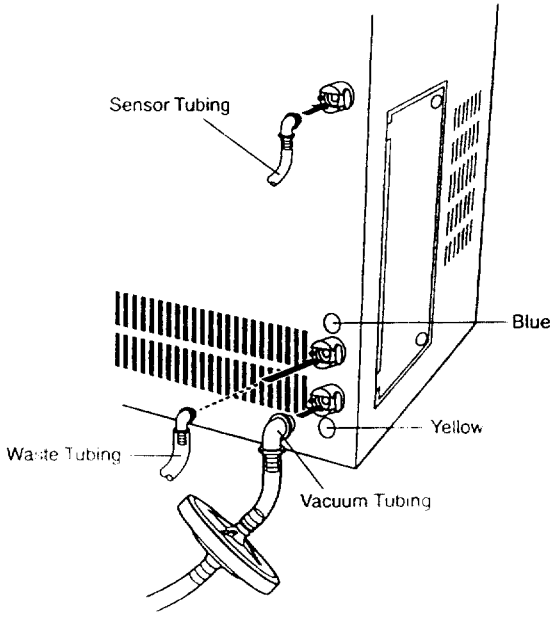
SECTION E

CONNECTING THE WASTE BOTTLE

At no time should bleach be present in the Waste Bottle while it is connected to the ThinPrep Processor. Refer to Chapter 5, *Maintenance* for details regarding the use of bleach.

1. The waste bottle should be placed at the same height or below the ThinPrep Processor. Do not place the waste bottle above the instrument.
2. Ensure that the waste bottle cap is tightly secured. The waste bottle must rest in an upright position. Do not allow the waste bottle to lay on its side.
3. Locate the three waste bottle connections at the rear of the ThinPrep Processor. Refer to Figure 2-5. Ensure that the buttons of the connectors are in the down/inward position.

Figure 2-5 Waste Tubing Connections



4. Connect the color coded waste tubing connectors to the corresponding connectors located in the rear of the ThinPrep Processor. When the proper connection has been established, the buttons on the connectors pop up/outward with a click sound. It may be necessary to push the button in before placing the waste tubing connector into the instrument connector.

Do not attempt to mismatch tubing connection. This may result in damage to your processor.

Always empty the waste bottle before it reaches the maximum liquid level line. Follow the procedure in Chapter 5, *Maintenance*.

SECTION F

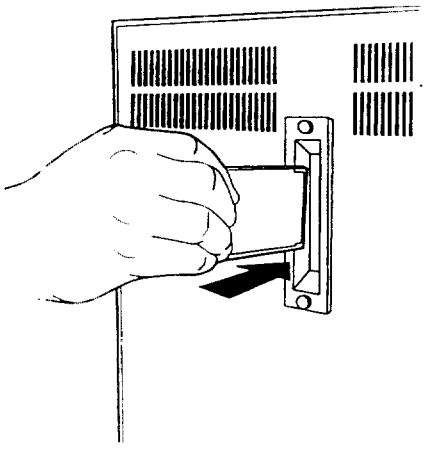
INSERTING THE PROGRAM MEMORY CARD

1. Confirm the power to the unit is off.

ALWAYS turn off the power before inserting or removing the Program Memory Card.

2. Locate the receptacle for the Program Memory Card (PMC) in the center of the rear panel of the ThinPrep Processor.
3. Orient the PMC as indicated by the arrows on the label of the card.
4. Insert the PMC into the unit as shown in figure 2-6. Continue to insert the card until the small black button at the top of the receptacle snaps out. If the PMC does not enter the unit smoothly, do not force it into the Thin Prep Processor socket.

Figure 2-6 Inserting the Program Memory Card



5. To remove the PMC, simply depress the black button at the top of the receptacle and gently remove the PMC.

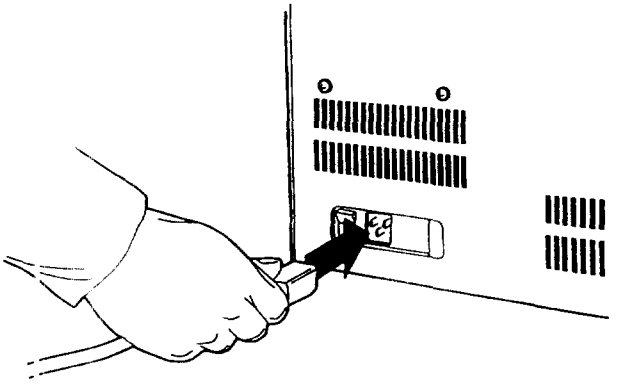
SECTION G

CONNECTING THE POWER CORD

Turning the power on before instructed to do so can damage the instrument and invalidate your warranty.

1. Ensure that the power switch, located on the rear of the ThinPrep Processor, is in the "O" (Off) position. For "Off", the top half of the toggle power switch is in the "out" position (protrudes).
2. Insert the power cord into the power receptacle located on the rear of the ThinPrep Processor next to the power switch. Refer to Figure 2-7.
3. Connect the power cord to a 3-prong grounded outlet.

Figure 2-7 Connecting the power cord



4 The ThinPrep Processor is designed with an automatic line voltage detection feature. This feature eliminates the need to manually change the system line voltage setting to meet your specific requirements. The instrument will automatically adapt to any line voltage between 100 – 120 VAC and 220 – 240 VAC.

Do not attach a cable to the 9-pin connector on the rear of the instrument. This connector is available for diagnostic purposes only.

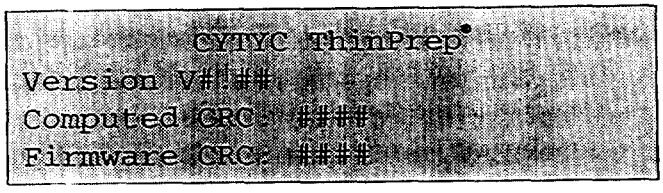
The ThinPrep Processor is fused internally. No user accessible fuse is available.

SECTION H

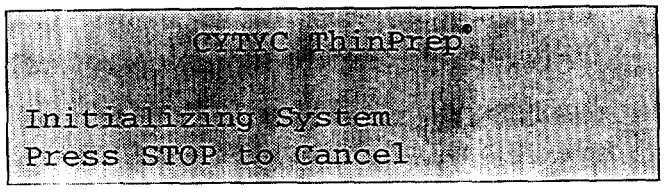
TURNING ON YOUR THINPREP PROCESSOR

1. Confirm that the internal securements have been removed from the instrument before proceeding with this procedure. Refer to Section D, for more information.
2. With the door to the ThinPrep Processor closed, turn the toggle power switch, located on the right rear of the ThinPrep Processor, to the "1" (ON) position. For "On", the top half of the toggle power switch is in the "in" position.
3. As the power is applied to the instrument, the control panel will display the following sequence of messages. If a different message appears in the display, follow the instructions on the control panel display or refer to Chapter 4, *Troubleshooting,* of this manual.

This message will appear for approximately four seconds:



At this point the system initializes all mechanisms while displaying this message for approximately four seconds.



After initialization, the system calibrates all pressure sensors while displaying this message for approximately twenty seconds:

```
Pressure sensor
calibration in
progress.
Please wait.
```

If the system initialization and calibration were successful, the control panel display will read:

```
Main Menu: Select
1-SUPER              4-GYN
2-FLU/FNA
3-MUCOID          ↓- MORE
```

The above message indicates that the system is in idle mode.

4. Leave the power to the ThinPrep Processor on all the time. It is not necessary to turn it off unless instructed to do so for trouble-shooting or maintenance procedures
5. The ThinPrep Processor pressure sensor calibration occurs several times while the power is on:
   - at power up
   - 15 minutes after power up
   - 2 hours after power up
   - every 8 hours thereafter

SECTION 1

RUN A BLANK SAMPLE

When operating the ThinPrep Processor for the first time, it is important to run a sequence using a blank PreservCyt Solution vial (no cells) to ensure that the system is fully functional. Read Chapter 3 *Operating Instructions* of this manual before proceeding with the procedure below.

1. Load a PreservCyt Solution vial (no cells) into the processor.
2. Attach a TransCyt Filter to the filter cap and load this assembly into the processor.
3. Load a ThinPrep Slide into the processor.
4. Load an empty fixative bath vial into the processor.
5. Close the door.
6. Press key 4 to start the GYN sequence.
7. The instrument will now process the blank PreservCyt Solution vial.
8. Upon successful completion of the sequence, the slide will be in the fixative bath vial and the display will read:

```
COMPLETE: NOTE

Sample is dilute
Please press ENTER
```

If any other message is displayed, record the message and refer to Chapter 4, *Troubleshooting,* of this manual.

9. Press the ENTER key and following message appears:

```
COMPLETE

Remove Filter
Remove Fix Bath
```

10. Open the door.
11. Remove the filter cap and TransCyt Filter.

12. Remove the fixative bath vial containing the slide.
13. Remove the PreservCyt Solution vial.
14. The installation of the instrument is complete. The ThinPrep Processor is now ready for slide preparations. Read Chapter 5, *Maintenance,* of this manual before proceeding with additional slide preparations.

Chapter Three

Operating Instructions

SECTION A

INTRODUCTION

This section provides instructions for operating the ThinPrep Processor. The following topics are covered in this section:

SECTION B: Material Requirements

SECTION C: Pre-Operation Checklist

SECTION D: Overview of Loading Processor

SECTION E: Loading the PreservCyt Sample Vial

SECTION F: Loading the TransCyt Filter

SECTION G: Loading the ThinPrep Slide

SECTION H: Loading the Fixative Bath Vial

SECTION I: Closing the Door

SECTION J: Selecting and Initiating a Sequence

SECTION K: Unloading the ThinPrep Processor

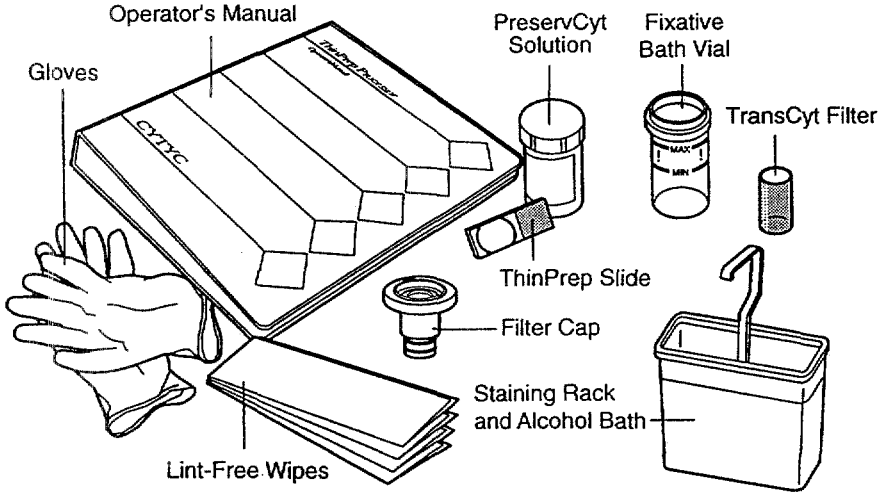
SECTION L: Interrupting the Slide Preparation Process

SECTION M: Status and Maintenance Screens

SECTION
B

MATERIAL REQUIREMENTS

Figure 3-1 The required materials



The **PreservCyt Solution vial** is a plastic vial that contains an alcohol-based preservative solution that preserves cells from all body sites for up to three weeks at room temperature. For more information on PreservCyt Solution, refer to Chapter 7, *Cytyc PreservCyt Solution.*

The **TransCyt Filter** is a disposable plastic cylinder that is open at one end and has a **filter membrane** bonded onto the other end. The filter membrane has a flat, smooth, porous surface.

The **filter cap** is a plastic cap that fits onto the open end of the TransCyt Filter and mounts the TransCyt Filter into the processor.

The **fixative bath vial** is a plastic vial that should be filled with standard laboratory fixative alcohol. After the ThinPrep Processor transfers cells onto the slide, it automatically ejects the slide into the fixative bath vial.

The **ThinPrep Slide** is a high quality, pre-cleaned glass microscope slide with a defined screening area and a larger labeling area. The slide is specifically designed for use with the ThinPrep Processor.

Supplies used in the ThinPrep 2000 System are those designed and supplied by Cytyc Corporation specifically for the ThinPrep 2000 System. These include PreservCyt Solution vials, TransCyt Filters, and ThinPrep Microscope Slides. These supplies are required for proper performance of the system and cannot be substituted for gynecologic use. Product performance will be compromised if other supplies are used. After use, supplies should be disposed of in accordance with local, state, and federal regulations.

The **ThinPrep Processor Operator's Manual** contains detailed information about the ThinPrep Processor, such as the principles of operation, operating instructions, specifications, and maintenance information. The manual also contains information on the solutions and materials required to prepare gynecologic slides with the ThinPrep Processor.

Disposable laboratory gloves – non-powdered gloves are recommended.

Lint-free wipes.

Alcohol bath with slide staining rack and standard laboratory fixative alcohol.

SECTION C

PRE-OPERATION CHECKLIST

The following conditions should be checked before preparing a slide on the ThinPrep Processor.

- Waste bottle – Make sure the fluid level of the waste bottle is below the "MAX" fill line of the bottle. Refer to Chapter 5, *Maintenance*, Section B, Emptying Waste Bottle, for emptying instructions.
- Idle mode – Confirm that the ThinPrep Processor is powered on and in idle, or Main Menu, mode. If the Main Menu is not displayed, follow the instructions on the display until the idle mode appears. If the system's power is off, refer to Chapter 2, *Installation and Specifications*, for turning system power on.
- Filter seal O-rings – Make sure that the two O-rings at the base of the filter cap are not dry, cracked, or in need of lubrication. Refer to Chapter 5, *Maintenance,* for lubrication and/or replacement instructions.
- Disposable laboratory gloves – Always wear disposable laboratory gloves and other lab safety garments when operating the ThinPrep Processor.

Note: Once sample has been added to a PreservCyt *Solution* vial, the vial is then designated as a PreservCyt *Sample* vial.

SECTION D

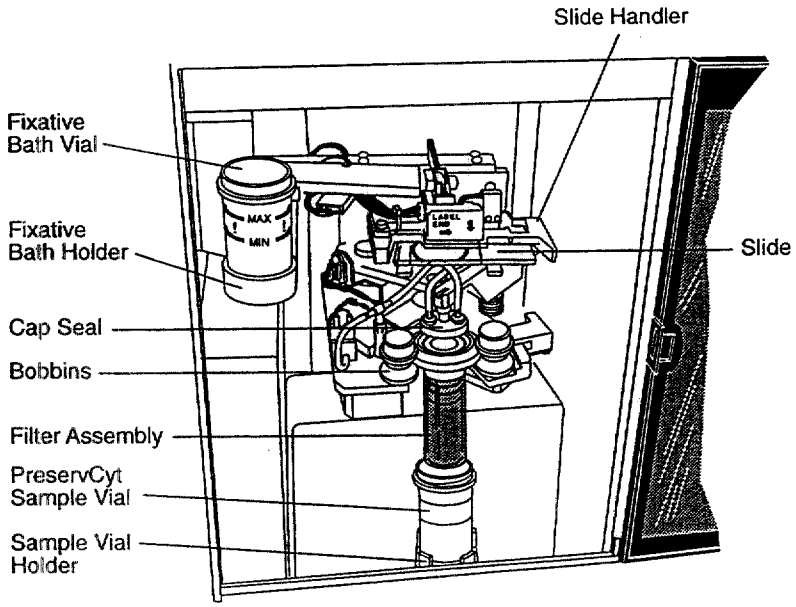
OVERVIEW OF LOADING PROCESSOR

The next four sections describe in detail the methods for loading the ThinPrep Processor. The following supplies must be loaded into the processor before initiating a sample run:

- PreservCyt Sample vial
- TransCyt Filter
- ThinPrep Slide
- Fixative bath vial

The figure below shows the ThinPrep Processor after loading of the supplies is complete.

Figure 3-2 ThinPrep Processor loaded with supplies

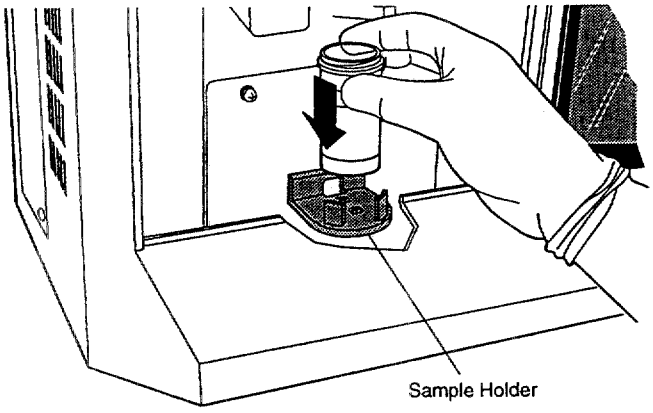


SECTION E

LOADING THE PRESERVCYT SAMPLE VIAL

1. Open the ThinPrep Processor door by gripping the door tab and sliding it gently to the right until it is completely open.
2. Confirm that the sample holder, fixative bath vial holder and slide handler are empty.
3. Remove the cap from the PreservCyt Sample vial.
4. Gently place the PreservCyt Sample vial into the sample holder until the bottom of the vial rests on the sample holder base. Refer to Figure 3-3.
5. The vial will remain loose in the sample holder until the process begins. The system will automatically grasp the vial during processing.

Figure 3-3 Loading the PreservCyt Sample vial.



SECTION F

LOADING THE TRANSCYT FILTER

1. Remove a new TransCyt Filter from the storage tray by grasping the sides of the cylinder.

Never touch the filter membrane of the TransCyt Filter.

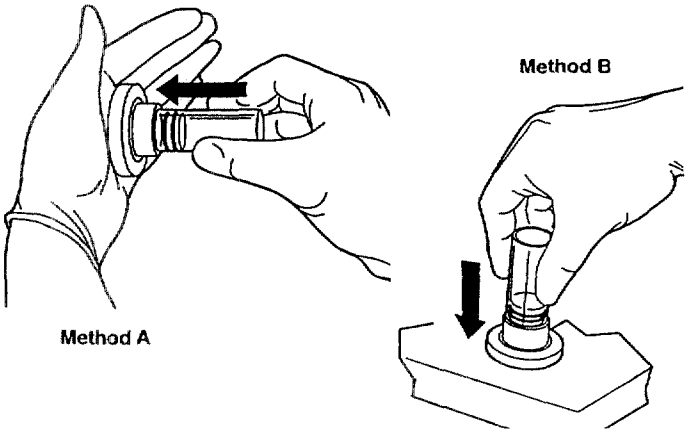
2. There are two different techniques for mating the TransCyt Filter and filter cap. This configuration of the two parts is called a filter assembly.

   Method A:
   Hold the filter cap in the palm of one hand and the TransCyt Filter in the other hand as shown in Figure 3-4. Insert the TransCyt filter.

   Method B:
   Place the filter cap on the bench and hold the TransCyt Filter in one hand. Insert the TransCyt Filter.

Using a slight twisting motion may be helpful with either technique. The filter seal O-rings should be lightly greased. Refer to Chapter 5, *Maintenance*, Section D.

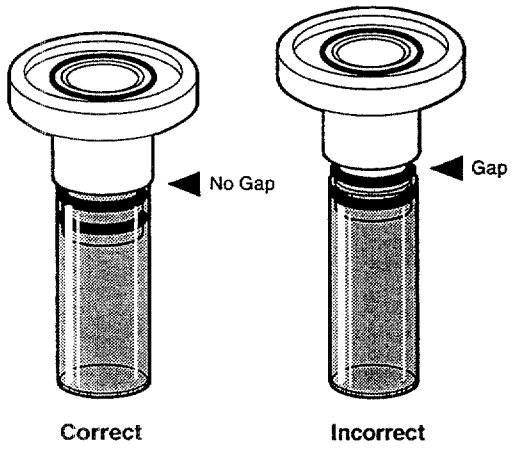
Figure 3-4 Assembling the filter cap and filter.



3. Ensure there is no visible gap between the TransCyt Filter and the filter cap as shown in Figure 3-5.

   The TransCyt Filter must seat against the filter cap lip.

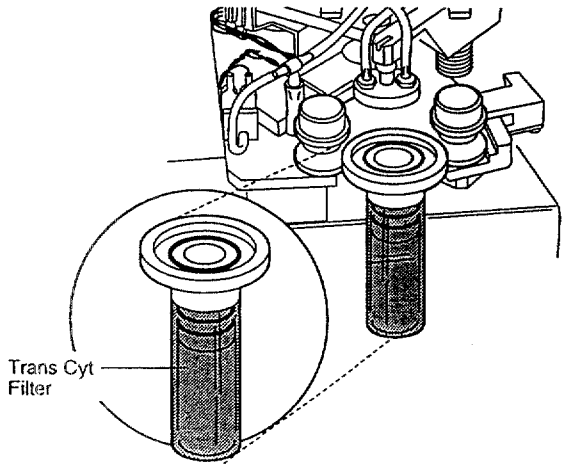
Figure 3-5 Correct filter cap-to-filter assembly



4. Insert the filter assembly into the instrument.

   Hold the filter assembly by the TransCyt Filter cylinder and place the angled edges of the filter cap against the two front bobbins as shown in Figure 3-6.

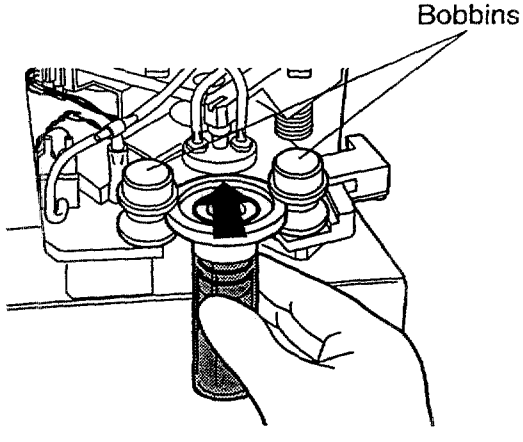
Figure 3-6 Positioning the filter cap in the bobbins



5. Keeping the filter assembly level, push it straight into the instrument. The right bobbin will move to the right as the filter assembly is inserted. The filter assembly is completely seated when the right bobbin moves back to the left and the two front bobbins hold the filter assembly in the processor. Refer to Figure 3-7.

   When properly loaded, the filter cap is level inside the instrument and the filter cylinder is above the PreservCyt Sample vial and slightly to the left. If the positioning of the filter assembly does not correspond to this description, remove it and try again. The filter assembly will easily rotate in the bobbins when properly seated.

Figure 3-7 Loading the filter assembly

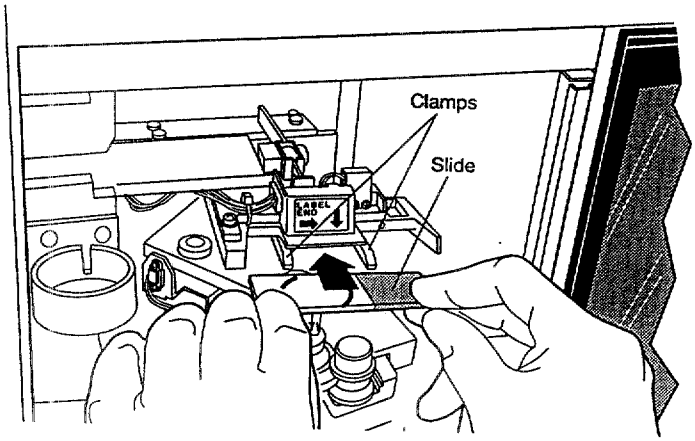


SECTION G

LOADING THE THINPREP SLIDE

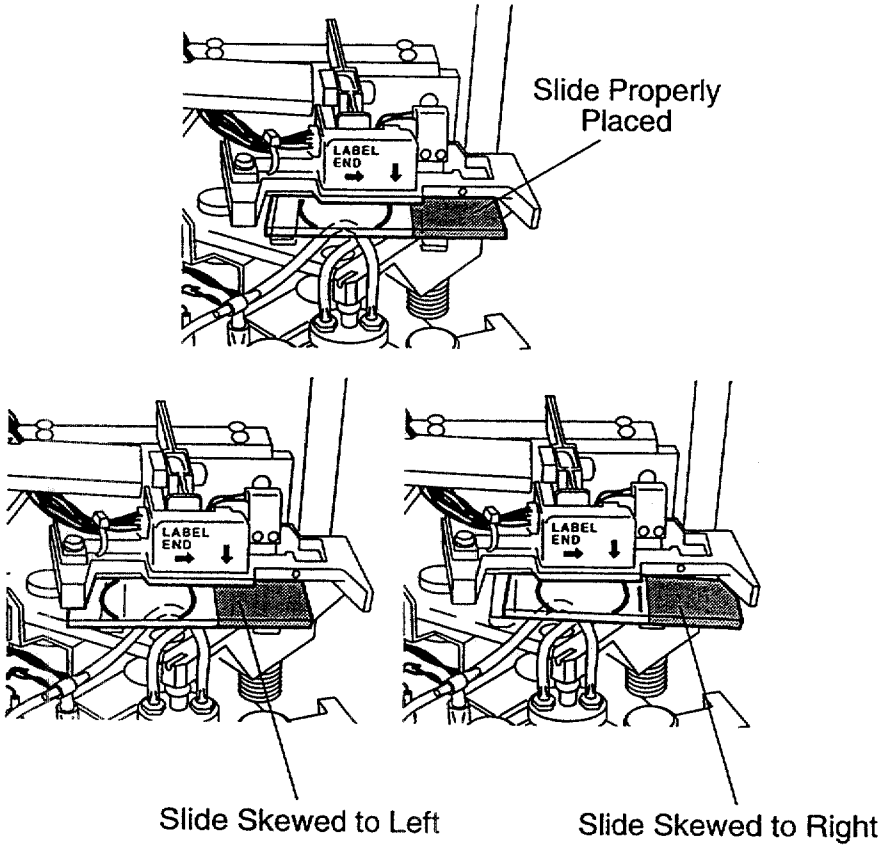
1. Label the ThinPrep slide with patient's identification information. Use the frosted area of the slide. When using an adhesive label, ensure that the label is completely adhered to the slide and that there are no overhanging edges.
2. Using two hands, hold the slide by the two front corners with your index fingers and thumbs as shown in Figure 3-8. Be sure not to touch the slide within the defined screening area. Place the label end to the right and facing down.
3. Insert the slide. Using the slide to push the spring-loaded clamps down, insert the slide halfway under the upper guide block and over the spring-loaded clamps, then release the slide. Refer to Figure 3-8.

Figure 3-8 *Inserting the slide onto the clamps*



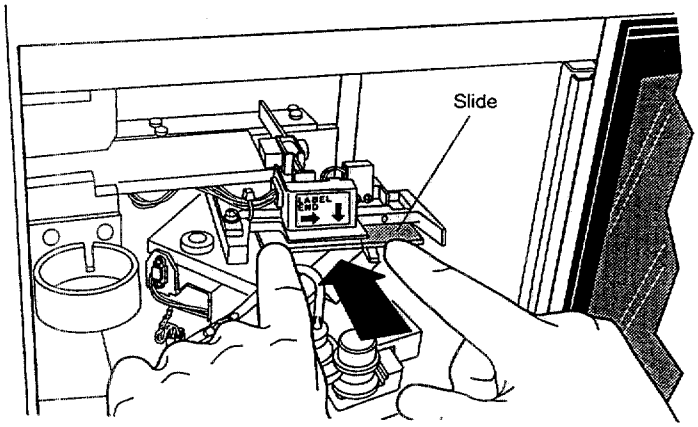
4. The slide should now rest *on top of* the two clamps and *under* the upper guide block as shown in Figure 3-9.

Figure 3-9 *Correct/Incorrect slide insertion*



5. To fully insert the slide, place your index fingers against the exposed edge of the slide and push the slide in until it does not go any further, as shown in Figure 3-10. The slide handler clamps grasp the slide when the slide is seated correctly and the slide moves up slightly behind the upper guide block.

Figure 3-10 Inserting the slide fully



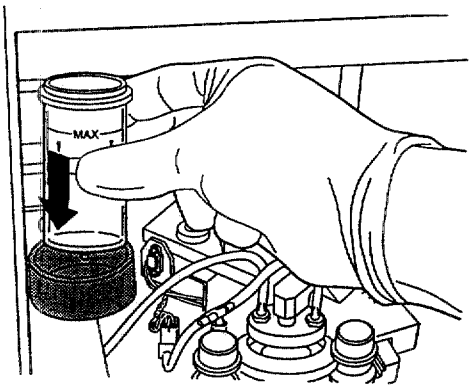
Note: To remove a slide, press down on the front edge of the slide. Gently pull the slide toward you.

SECTION H

LOADING THE FIXATIVE BATH VIAL

1. Fill a fixative bath vial with standard laboratory fixative alcohol until the fluid level is between the "MIN" and "MAX" marks on the vial.
   If the staining protocol requires alternative fixation methods, leave the fixative bath vial empty or fill it with the appropriate fixative solution.
   Change the contents of the fixative bath vial at least every 100 slides or daily, whichever occurs first.
2. Place the fixative bath vial into the fixative bath holder until the bottom of the vial rests on the base of the holder. Refer to Figure 3-11. Ensure that the fixative bath vial is completely seated.

Figure 3-11 Loading the fixative bath vial

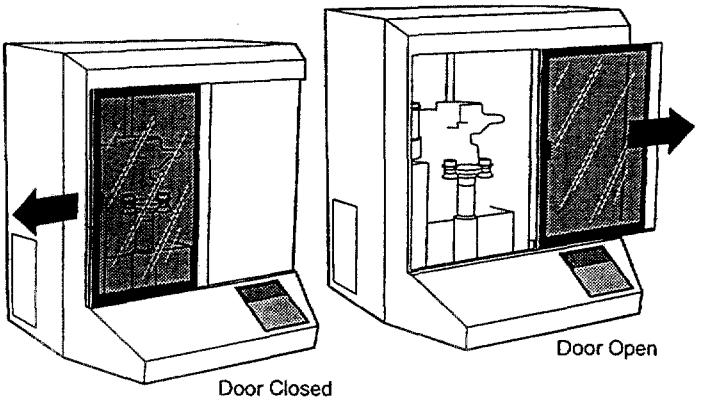


SECTION 1

CLOSING THE DOOR

To close the door, grasp the door tab and slide it completely to the left. The instrument will not operate if the door is open. The door must never be opened during instrument operation. If the door is opened after processing begins, the sequence will abort. The system will wait until the door is closed before system recovery will occur.

Figure 3-12 *Door opening and closing*



Do not open the door during processing. Depending on where a sequence is interrupted, cells may be lost or air-dried during recovery.

SECTION J

SELECTING AND INITIATING A SEQUENCE

The ThinPrep Processor has several program modes in its program card. There are two primary types of modes:

1. Sample processing sequences
2. Diagnostic

The sample processing sequences are used to process different kinds of specimens. The diagnostic modes are used to display the status of the instrument or to perform maintenance procedures. The Main Menu, shown below, is displayed whenever the instrument is in its idle state.

```
Main Menu: Select
1-SUPER                4-GYN
2-FLU/FNA
3-MUCOID               ↓- MORE
```

The Main Menu contains the three sequences for sample processing. To view the diagnostic modes, push the down arrow key and the menu will change to the following:

```
Main Menu: Select
6-STATUS               8-TEST
7-MAINT
STOP-PREVIOUS MENU
```

A description of the sequences is in Table 3-1.

106

Table 3-1 ThinPrep Processor Sequences and Modes

Key Number	Description
1	SUPERFICIAL SAMPLES Includes non-mucoid, superficial cell samples such as oral cavity samples, nipple secretions, skin lesions (Tzanck Test) and buccal samples.
2	FLUIDS AND FNA SAMPLES Includes non-mucoid body cavity fluids and fine needle aspirates.
3	MUCOID SAMPLES Includes sputum samples, bronchial brush and wash samples, and gastrointestinal samples.
4	GYNECOLOGIC SAMPLES Includes cell samples from the ectocervix and the endocervix. Use this sequence for the ThinPrep Pap Test.
6	STATUS
7	MAINTENANCE
8	TEST

To initiate a sample processing sequence, simply press the key corresponding to the desired sequence. The sequence will begin immediately after the key is pressed. If an incorrect sequence is selected, press the STOP key to abort the sequence. At the end of the sequence, the display will return to the Main Menu.

Do not open the door during processing. Depending on where a sequence is interrupted, cells may be lost or air-dried during recovery.

To view the diagnostic modes, push the down arrow key from the Main Menu and the options will be displayed. To return to the idle mode and the sample processing sequences, push the STOP key. To initiate the diagnostic modes, push the number of the desired option. The diagnostic modes return to the previous screen automatically upon their completion or after the operator pushes the STOP key.

If the ThinPrep Processor detects an error condition during any sequence, the sequence will abort, the system will attempt to recover and a message will be displayed. Refer to Chapter 4, *Troubleshooting*, for more information.

SECTION K

UNLOADING THE THINPREP PROCESSOR

1. Open the door by sliding it to the right.
2. Remove the fixative bath vial containing the prepared slide from its holder. It is necessary to remove the fixative bath vial from the holder after each slide is processed.

The fixative bath vial must be removed. Evaporating alcohol could create a fire hazard.

3. Remove the prepared slide from the fixative bath vial and deposit the slide into a staining rack in a bath containing standard laboratory fixative.

   Refer to Chapter 6, *Fixation and Staining*, for more information about slide fixation and staining.
4. Using the cross-contamination precautions listed below, remove the filter assembly and separate the TransCyt Filter from the filter cap (a slight twisting motion may be helpful).

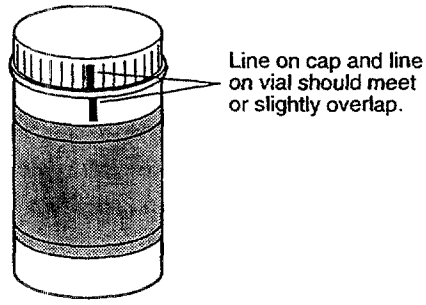
To reduce the possiblity of cross-contamination, use one of the following methods to remove the TransCyt Filter from the filter cap:

Method A:
Place a lint-free wipe around the TransCyt Filter to prevent contamination of your gloves while removing the filter assembly from the instrument and while separating the TransCyt Filter from the filter cap. Dispose of the lint-free wipe with the TransCyt Filter.

Method B:
Remove the TransCyt Filter from the filter cap and wipe off your gloves with lint-free wipe to remove any liquid or change your gloves after each slide preparation cycle.

5. Dispose of the used TransCyt Filter cylinder using appropriate laboratory procedures. **A TransCyt Filter must be used only once and cannot be reused.**
6. Remove the PreservCyt Sample vial from the instrument and recap it firmly. Be sure to line up the torque line on the cap with the torque line on the vial. Refer to Figure 3-13.

Figure 3-13 Capping the PreservCyt Sample vial



7. Do not discard the sample vial until it has been determined that no additional slides are needed. Refer to Chapter 7, *Cytyc PreservCyt Solution*, for information regarding solution disposal and sample storage.

SECTION L

INTERRUPTING THE SLIDE PREPARATION PROCESS

Ordinarily, the ThinPrep Processor slide preparation process should not be interrupted. However, if it is necessary to stop processing for any reason, use the following procedure to ensure the slide is not contaminated with another specimen.

1. Press the STOP key and wait until the display reads, RECOVERY COMPLETE.

   The ThinPrep Processor will halt the process with an audible tone and a message indicating that the STOP key was pressed will be displayed. The instrument will automatically recover and return the motors to their starting positions. The system will always attempt to return cellular material on the filter back into the sample vial during error recovery.
2. Press the ENTER key to stop the audible alarm and to return to the Main Menu.
3. Remove the fixative bath vial if it contains a slide, otherwise remove the ThinPrep Slide from the slide holder.
4. Remove the filter assembly.
5. Remove the TransCyt Filter from the filter cap if it is wet or damaged. Dispose of the TransCyt Filter using the appropriate laboratory procedures. Refer to Section K, *Unloading the ThinPrep Processor*, of this chapter.
6. Remove the PreservCyt Sample vial if it is not the correct specimen.

   Refer to Section E, *Loading the PreservCyt Sample Vial*, earlier in this chapter to restart the process.

SECTION M

STATUS, MAINTENANCE AND TEST SCREENS

The ThinPrep Processor has seven different Main Menu options which can be viewed by pressing the up and down arrow keys:

- **1-4:** Processing Sequences
- **6:** Status
- **7:** Maintenance
- **8:** Test

Section J of this chapter describes how to initiate the sequences. The purpose of this section is to describe the functions of Status, Maintenance, and Test. By pressing the down arrow key from the Main Menu the following appears:

```
Main Menu: Select
6-STATUS              8-TEST
7-MAINT
STOP - PREVIOUS MENU
```

6 – STATUS:

```
Status:
1 - COUNTERS
2 - ERROR HISTORY
3 - FIRMWARE VERSION
```

Pressing [6] from the Main Menu displays the following screen.

To return to the Main Menu, press STOP.

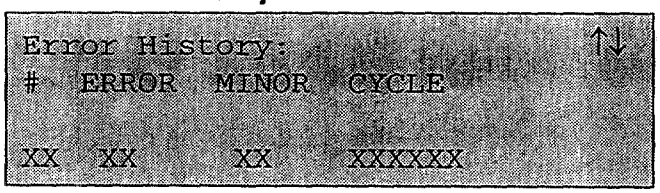
1 – Counters:

```
Sequence Counters:
1 - XXXXXX          4 - XXXXXX
2 - XXXXXX
3 - XXXXXX          T - XXXXXX
```

Pressing [1] displays the Sequence Counters. A number is displayed next to each sequence number which identifies the number of cycles for that particular sequence. The value next to the "T" is the total number of cycles on the processor. To return to the Status Menu, press STOP.

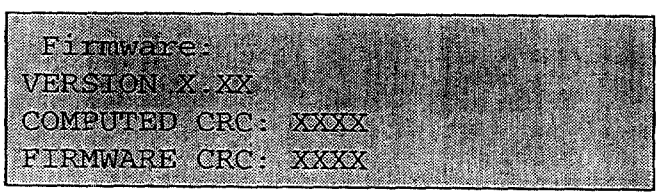
118

2 – Error History:



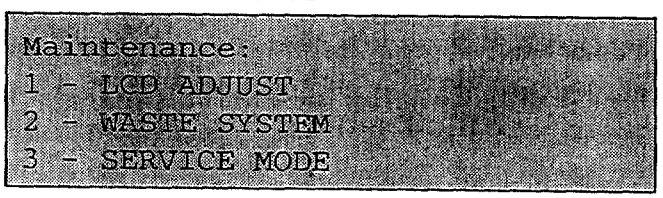
Pressing [2] displays the Error History screen. The system will store the last 50 error messages that occurred on the processor. Technical Service may ask you to access this screen during troubleshooting. The first column (#) is the counter, 1–50. The second column (ERROR) is the error code. The third column (MINOR) is the minor error number which often provides additional information on the source of the error. The last column (CYCLE) is the total cycle count of the processor when the error occurred. To return to the Status Menu, press STOP.

3 – Firmware Version:



Pressing [3] displays the Firmware screen. This screen allows the operator to view the version of the Program Memory Card in use without turning off the power and removing the card. Technical Service may access this screen during troubleshooting. To return to the Status Menu, press STOP.

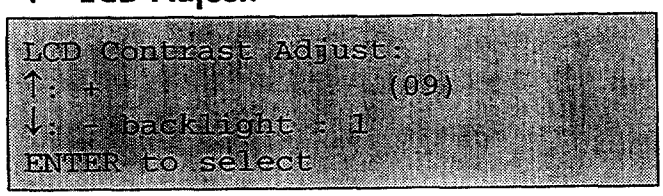
7 – MAINTENANCE:



Pressing [7] from the Main Menu displays the following screen.

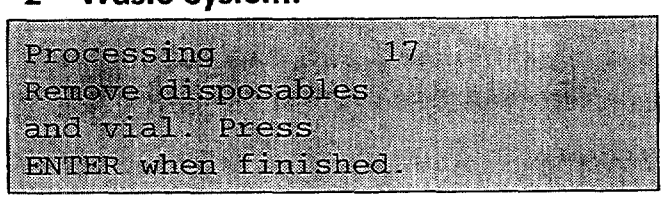
To return to the Main Menu, press STOP. The processor must be completely empty of supplies before continuing with Maintenance.

1 – LCD Adjust:



Pressing 1 displays the LCD Contrast Adjust screen. A number is displayed in the parentheses from 00 to 15. Use the up and down arrow keys to adjust the contrast to an acceptable level and then press the ENTER key to save the change and to return to the Maintenance Menu.

2 – Waste System:



Pressing 2 initiates the waste system maintenance mode. It is critical to remove the fixative bath vial, filter, slide, and sample vial before continuing. After pressing ENTER to continue, three things occur:

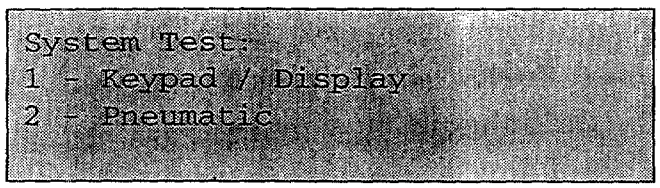
- *Waste bottle vacuum vents to atmosphere* – The waste bottle bleeds off to allow the operator to more easily remove the cap off the waste bottle for emptying of its contents. See Chapter 5, *Maintenance*, Section B.
- *Rotating plate in processor inverts* – The rotating plate inverts to allow the operator to more easily clean the underside of the cap seal. See Chapter 5, *Maintenance*, Section G.
- *Sample vial holder rises* – The sample vial holder rises to allow the operator to more easily clean under the holder. See Chapter 5, *Maintenance*, Section H.

When the maintenance operation is complete, the operator must press ENTER with the door closed to return to the Main Menu.

3 – Service Mode:

Pressing 3 initiates the Service Mode screen. This Service Mode is for Cytyc use only. Technical Service may ask you to access this screen during troubleshooting. To return to the Main Menu, press STOP.

8 – TEST:



Pressing [8] from the Main Menu displays the following screen. To return to the Main Menu, press STOP.

1 – Keypad / Display:

This test is used to confirm proper operation of the keypad and display. Pressing [1] initiates the Keypad / Display Test screen. Press all of the keys on the keypad and confirm that the corresponding character is changed on the display. Press the STOP key last to end the test. If any keys fail to respond, call Cytyc Technical Service.

2 – Pneumatic:

This test is used to confirm the proper operation of the entire pneumatic system. Cytyc recommends running this 5-minute test on a weekly basis. The results of this test may notify the operator to perform certain maintenance procedures or warn them that instrument service is required.

Pressing [2] prompts the user to load the sealed cylinder into the instrument. Press ENTER to initiate the test. The test will automatically end if any errors occur and the operator will be notified of the area of concern. Once the problem has been addressed, it is necessary to run the test again to ensure proper operation. If no errors occur, the test will end with a message which indicates a successful test.

Errors:	Action:
• CAP SEAL LEAK	Clean filter cap & cap seal
• WASTE PRESSURE FAILURE	Follow Troubleshooting for Waste Pressure Failure error
• ATM VALVE LEAK	Call Cytyc Technical Service
• QTO VALVE LEAK	Call Cytyc Technical Service
• POSITIVE PRESSURE FAILURE	Call Cytyc Technical Service
• NEGATIVE PRESSURE FAILURE	Call Cytyc Technical Service

- WASTE LINE CLOGGED Call Cytyc Technical Service
- – TANK LINE CLOGGED Call Cytyc Technical Service
- + TANK LINE CLOGGED Call Cytyc Technical Service
- QTO LINE CLOGGED Call Cytyc Technical Service

Chapter Four

Instrument Troubleshooting

SECTION A

INTRODUCTION

This section provides detailed troubleshooting procedures for problems that may occur during slide preparation. The procedures in this section are designed to help the operator to identify and correct the most common causes of error messages. If the problem cannot be corrected by the operator, these procedures can help Cytyc Technical Service to quickly identify the problem.

SECTION B

HOW TO USE THIS SECTION

This section lists all the ThinPrep Processor messages. The messages are divided into warnings and errors. The description of each message includes a reason for the message, possible causes, and a trouble-shooting flowchart.

Follow the three-step procedure listed below for any displayed message.

1. Record the message displayed on the ThinPrep Processor display panel before pressing the ENTER key.
2. Look up the message in the Contents listed on Page 4.3. If the message does not appear on page 4.3, call Cytyc Technical Service.
3. Follow the instructions in the troubleshooting procedure flowchart.

SECTION C

CONTENTS

119

Close Door to Continue Processing

Reason for Message

This message appears when the ThinPrep Processor has detected an open door condition during processing or error recovery. The processor will pause until the door is closed.

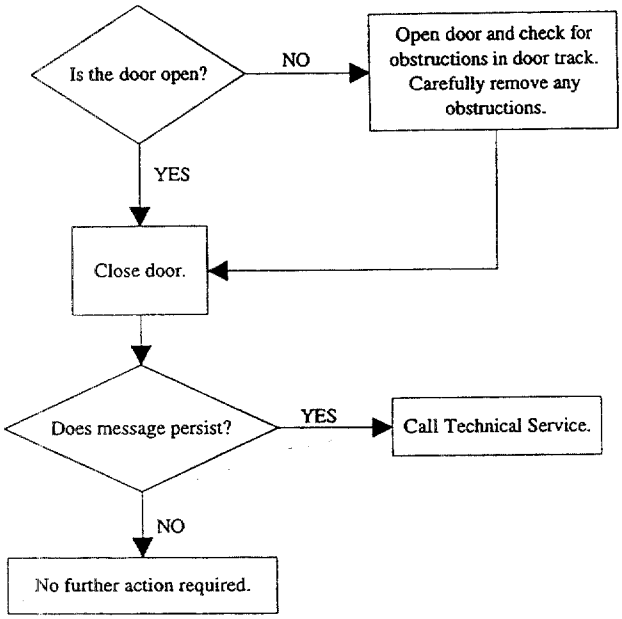
Possible Causes

- Door opened during processing or error recovery.
- Door not fully closed due to obstruction.
- System hardware malfunction.

Procedure

See flowchart on next page.

Close Door to Continue Processing



Insert Fix Bath to Continue Processing

Reason for Message

This message appears when the ThinPrep Processor does not detect the presence of the fixative bath vial. The processor will pause until the operator corrects the situation.

Note: The processor can only detect the pressure or absence of a fixative bath vial. It cannot determine if the fixative bath vial contains fixative solution.

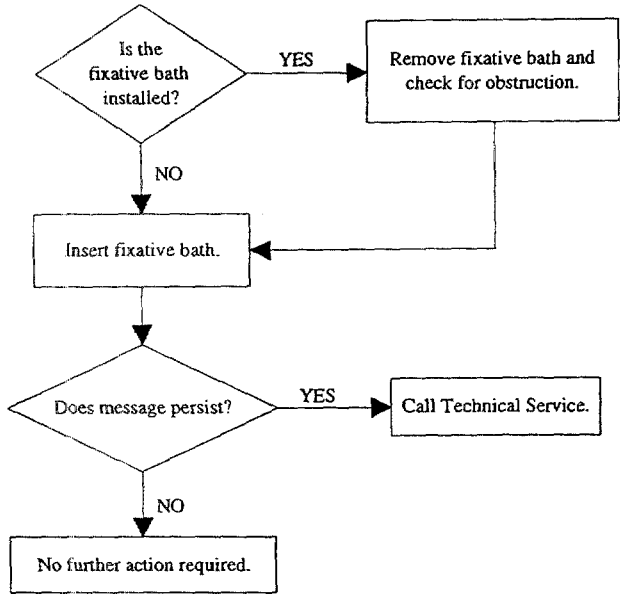
Possible Causes

- Fixative bath not installed.
- Fixative bath improperly installed due to obstruction.
- System hardware malfunction.

Procedure

See flowchart on next page.

Insert Fix Bath to Continue Processing



Insert Slide to Continue Processing

Reason for Message

This message appears when the ThinPrep Processor cannot detect the presence of a slide in the slide holder at the start of a sequence. The processor will pause until the operator corrects the situation.

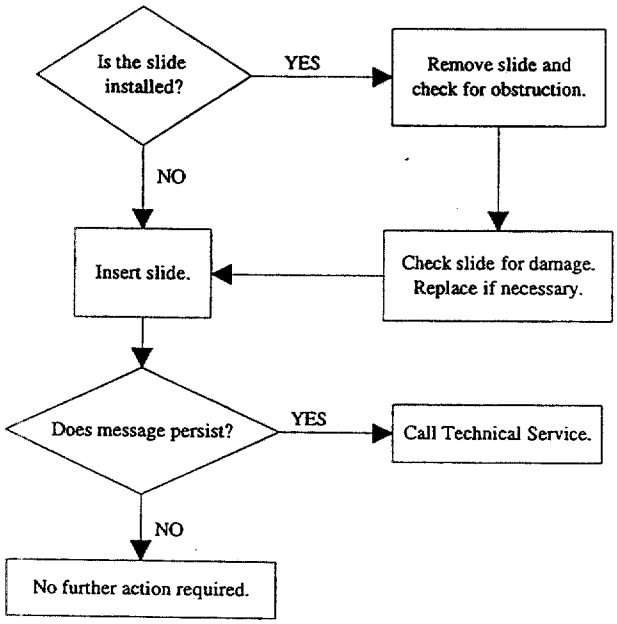
Possible Causes

- Slide not installed.
- Slide improperly installed due to obstruction.
- System hardware malfunction.

Procedure

See flowchart on next page.

Insert Slide to Continue Processing



Remove Filter

Reason for Message

This message appears when the ThinPrep Processor has completed processing a slide and the filter assembly has not been removed from the processor. The processor will pause until the operator corrects the situation.

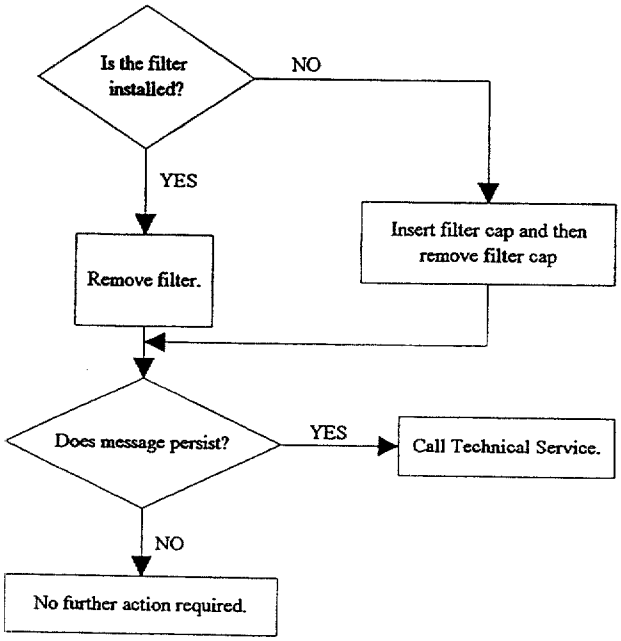
Possible Causes

- Filter not removed after last sequence.
- Error recovery requires filter removal.
- Filter cap was not removed by withdrawing it straight out of the bobbins.

Procedure

See flowchart on next page.

Remove Filter



Remove Fix Bath

Reason for Message

This message appears when the ThinPrep Processor has completed processing a slide and a slide has been deposited into the fixative bath vial. The processor will pause until the operator corrects the situation.

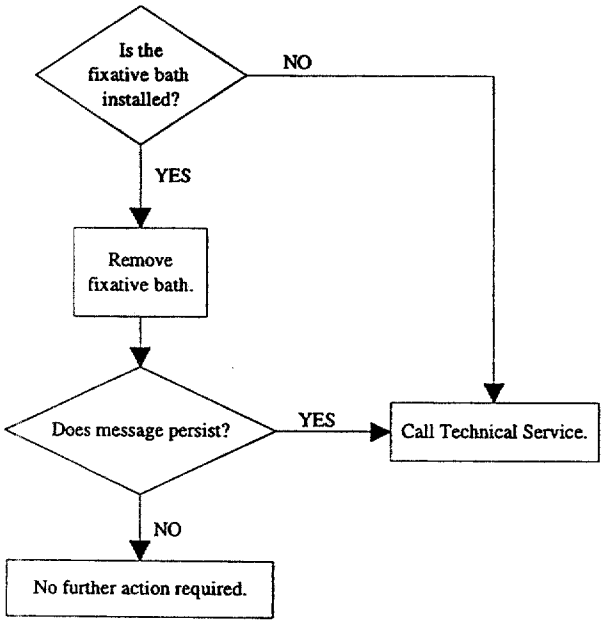
Possible Causes

- Fixative bath never removed after completed sequence.
- System powered on with fixative bath installed.

Procedure

See flowchart on next page.

Remove Fix Bath



Remove Slide

Reason for Message

This message appears when the ThinPrep Processor has completed processing a slide and the slide has not been ejected from the slide handler. This error generally occurs when another error condition has occurred which prevents the instrument from ejecting the slide. The processor will pause until the operator corrects the situation.

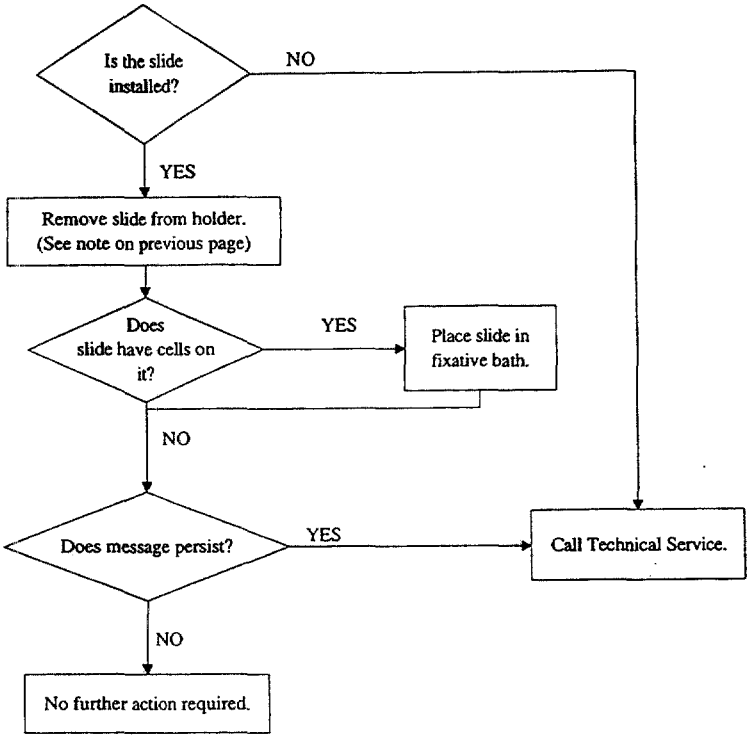
Possible Causes

- Error recovery requires slide removal.

Procedure

See flowchart on next page.

Remove Slide



Remove Slide to Continue Processing

Reason for Message

This message is designed to ensure that cell transfer occurs only once per slide. The slide from a previous run has not been ejected or a slide was present in the slide handler when the instrument power was turned on. The processor will pause until the operator corrects the situation.

Possible Causes

- System powered on with slide installed.

Procedure

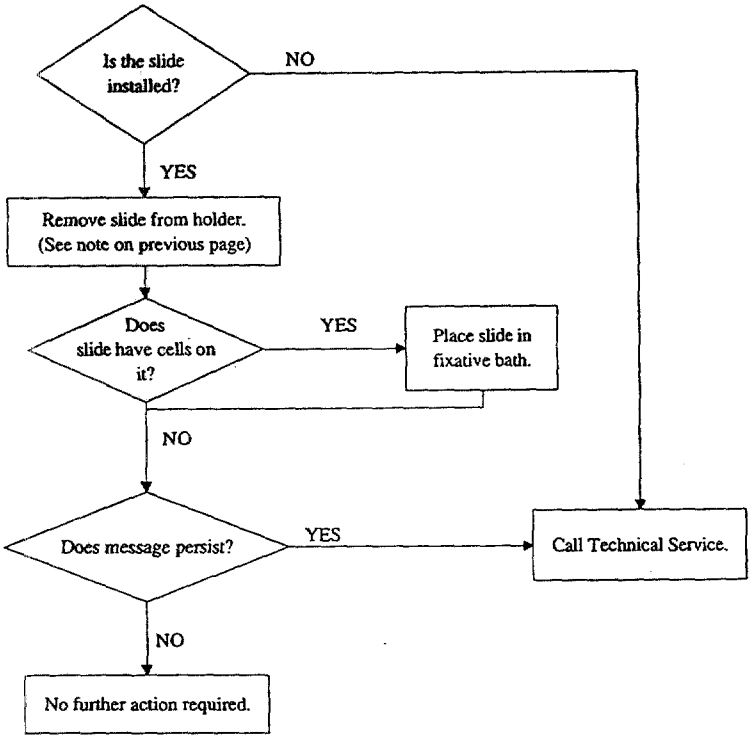
See flowchart on next page.

Notes

To remove a slide, push down on the front edge of the slide. While holding the slide by this edge, gently pull the slide out of the instrument.

If the slide is installed and it has cells on it, the cells on the slide are likely to be air-dried.

Remove Slide to Continue Processing



Sample is dilute

This message is displayed when most of the sample has been aspirated through the filter membrane, but the percentage of filter coverage has not reached the target coverage. This message is only a warning; the instrument continues to make a slide from the sample. Upon completion of the sequence, the instrument emits an audible alert until the operator presses the ENTER key. The slide should be stained and screened.

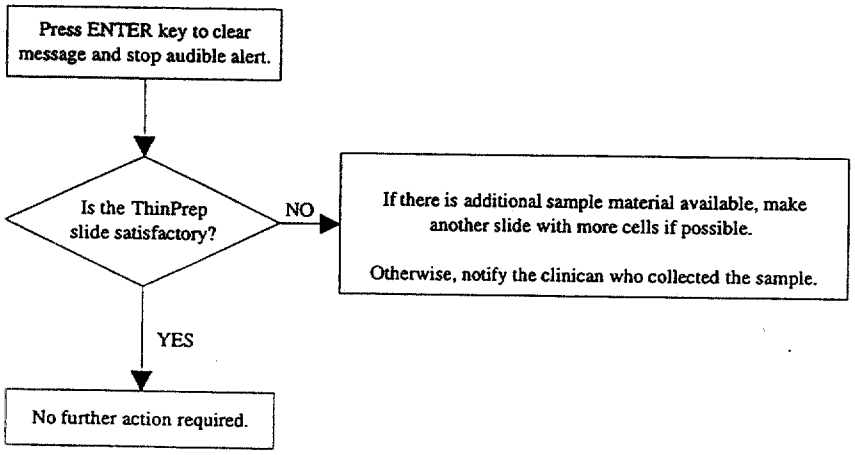
Reason for Message

There is a possibility of low concentration of cells in the sample.

Procedure

See flowchart on next page.

Sample is dilute



Evacuation Failure. Check Filter.

Reason for Message

This message appears when the ThinPrep Processor detects a failure to completely evacuate filtrate from the TransCyt Filter after cell collection is complete.

Possible Causes

- Waste bottle cap is not secure.
- Waste filter is wet.
- System hardware malfunction.
- Waste tubing is disconnected or obstructed at any point.
- Damaged TransCyt Filter.

Procedure

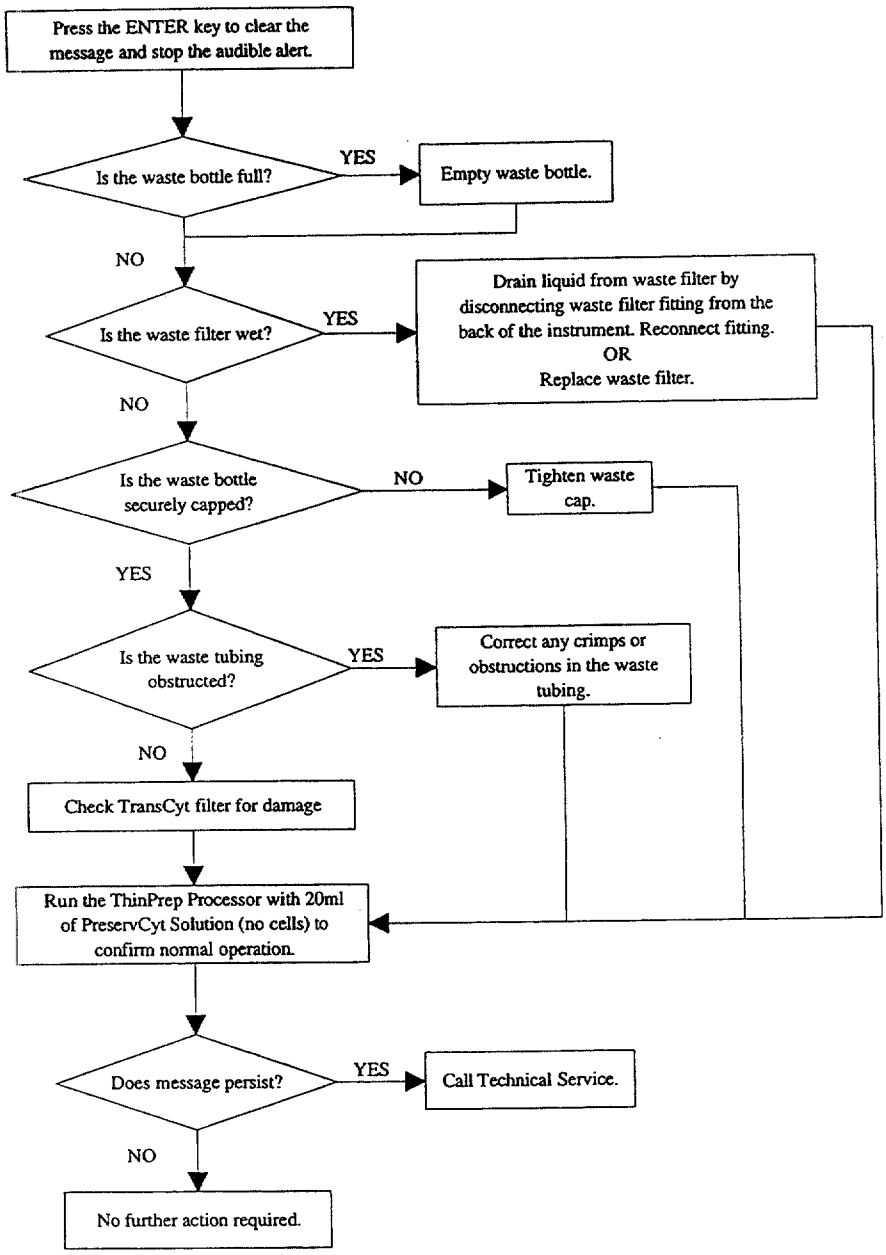
See flowchart on next page.

Notes

Check the waste bottle daily prior to beginning slide processing. Make sure that the fluid level does not exceed the "Max" mark on the waste bottle label.

If the waste bottle is overfilled, it may be necessary to remove the waste fitting with the waste filter from the rear of the instrument to allow the fluid to drain from the waste filter. Reattach the fitting and attempt to run a blank on the processor. If the error persists, replace the waste filter as described in Chapter 5, *Maintenance*, Section I.

Evacuation Failure. Check Filter.



Filter already wet.

Reason for Message

This message appears when the ThinPrep Processor cannot detect airflow throughout the TransCyt Filter prior to contact with the fluid. This is done to ensure that a previously used filter will not contaminate another sample.

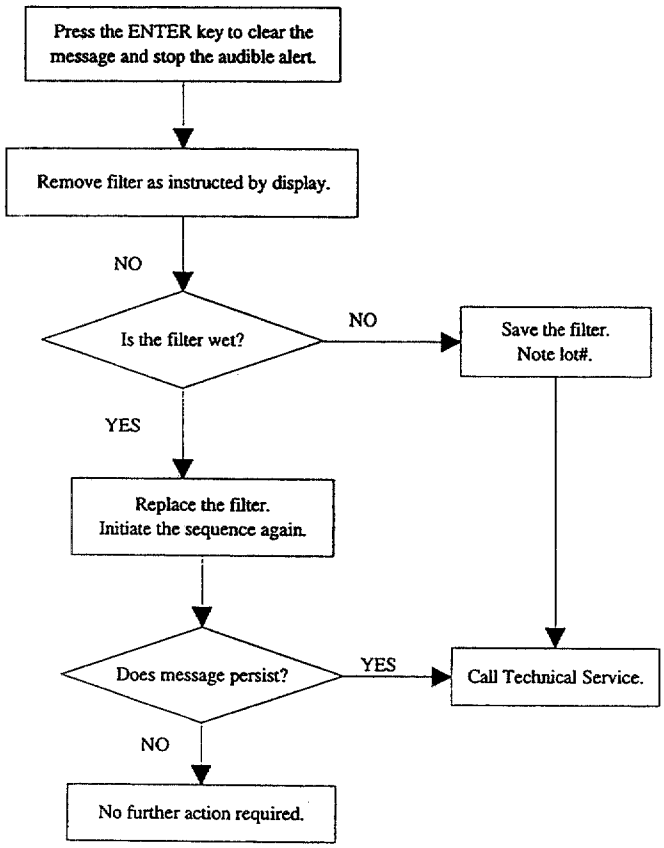
Possible Causes

- Wet TransCyt Filter.
- Obstructed TransCyt Filter membrane.
- System hardware malfunction.

Procedure

See flowchart on next page.

Filter already wet.



No fluid detected. Check filter and vial

Reason for Message

This message appears when the ThinPrep Processor cannot sense the appropriate liquid level in the PreservCyt Sample vial.

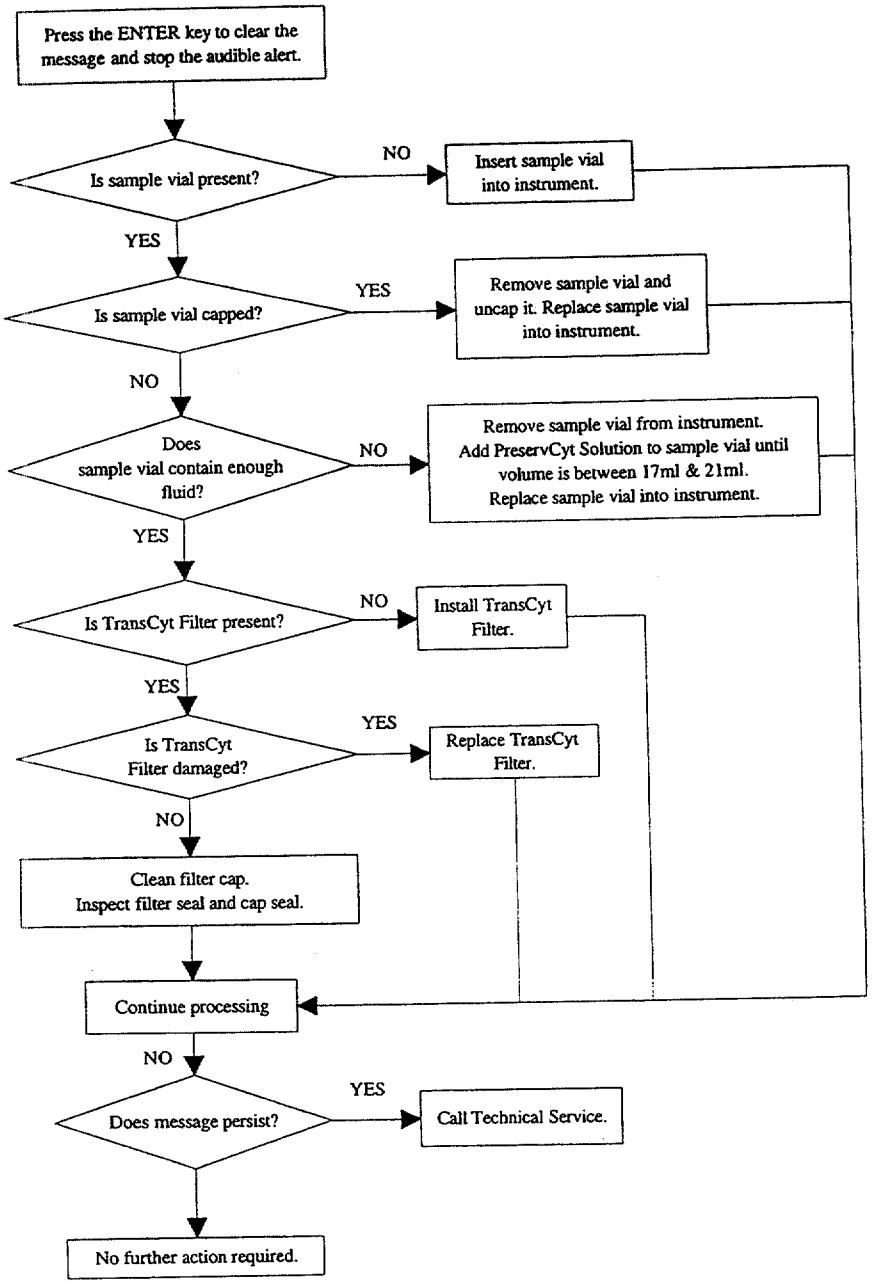
Possible Causes

- PreservCyt Sample vial missing.
- Fluid in PreservCyt Sample vial too low.
- TransCyt Filter not installed.
- Large hole in TransCyt Filter membrane.
- Obstruction preventing cap seal from seating properly.
- Damaged cap seal O-ring.
- Pinched or obstructed pneumatic tubing.
- System hardware malfunction.

Procedure

See flowchart on next page.

No fluid detected. Check filter and vial



Sample too dense. Dilute 20:1

This message is displayed when the sample is too dense for the instrument to make a satisfactory slide. This will halt processing and no slide will be made. This message is followed by an audible alert until the operator presses the ENTER key.

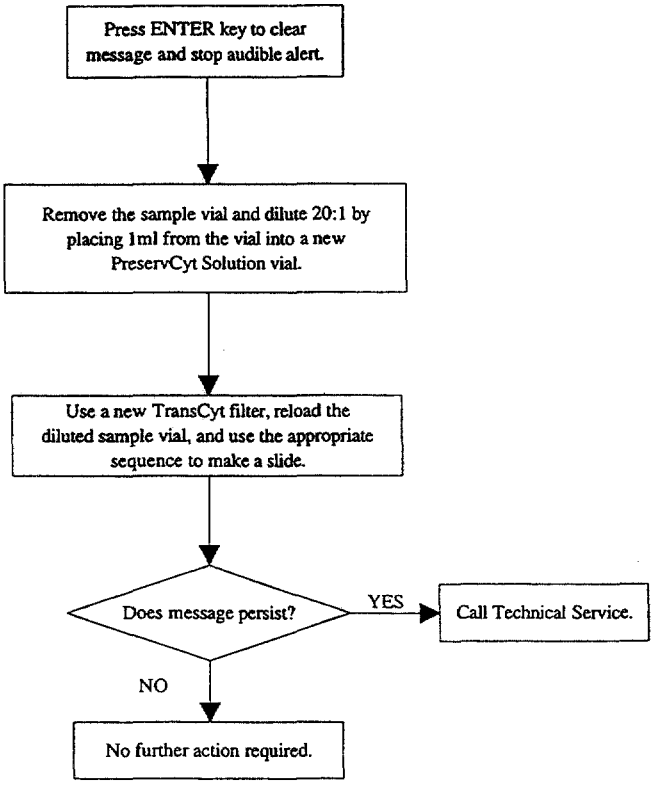
Reason for Message

There is a possibility of high concentration of material in the sample vial.

Procedure

See flowchart on next page.

Sample too dense. Dilute 20:1



Vial too full. 21mL max. allowed

Reason for Message

This message appears when the ThinPrep Processor detects the fluid level of the PreservCyt Sample vial too early.

Possible Causes

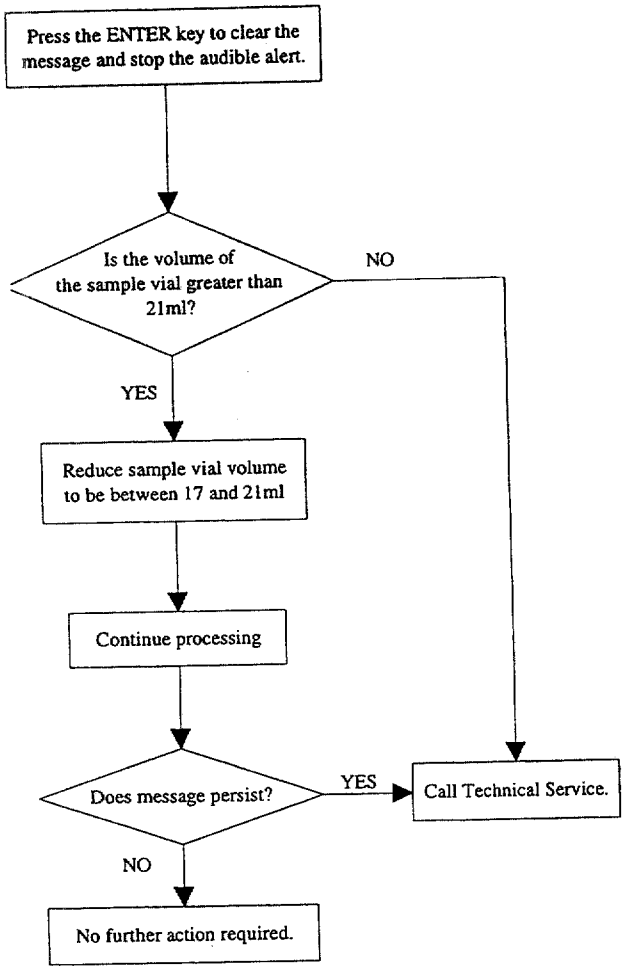
- Volume of PreservCyt Sample vial is greater than 21ml.
- System hardware malfunction.

Procedure

See flowchart on next page.

If it is necessary to reduce the sample vial volume to be between 17ml and 21ml, save any excess fluid in an appropriate container.

Vial too full. 21mL max. allowed



Waste System Failure

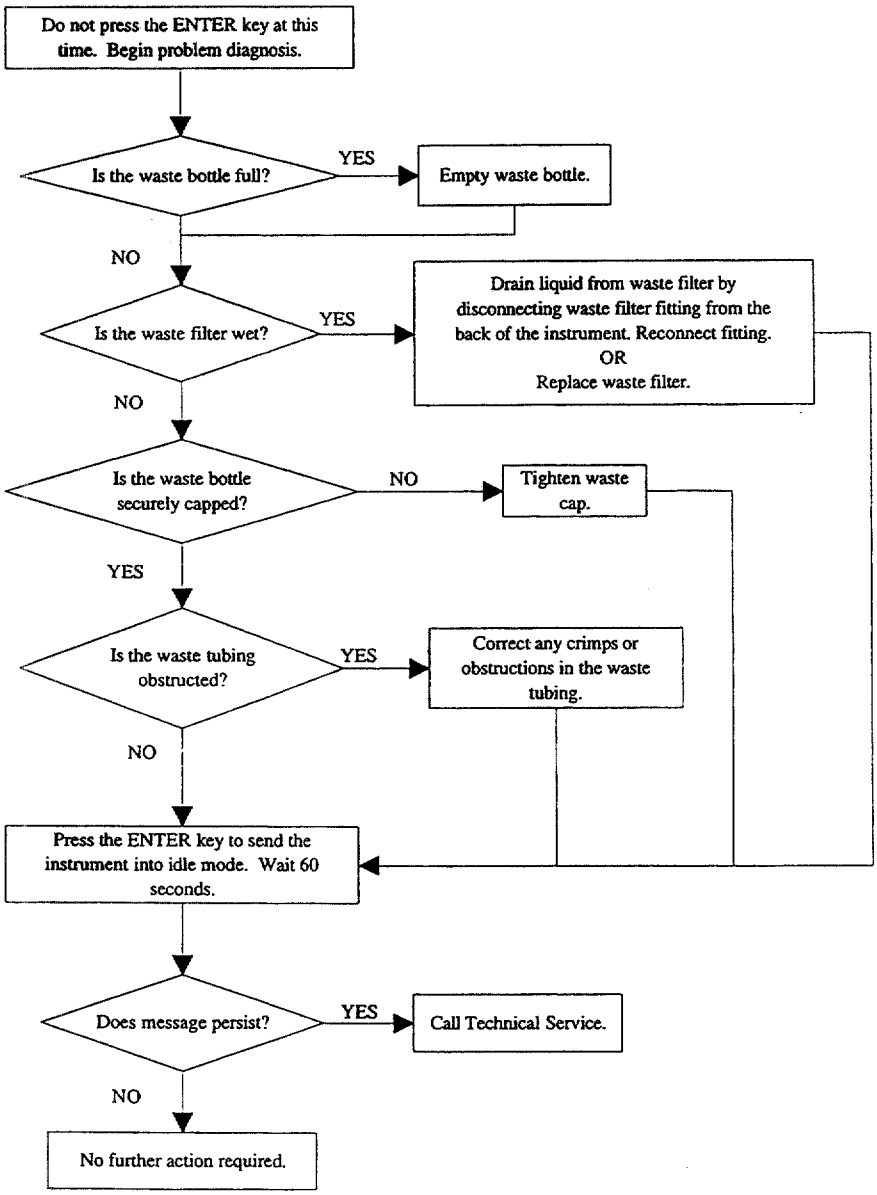
Reason for Message

This message appears when the ThinPrep Processor fails to detect its target negative pressure in the waste bottle during idle mode or at the start of a sequence.

Possible Causes

- Waste bottle cap is not secure
- Waste fittings are disconnected from back of instrument
- Waste tubing is disconnected or obstructed at any point
- System hardware malfunction
- Waste filter is wet

Waste System Failure



DOOR OPEN WHILE PROCESSING SAMPLE

Reason for Message

This message appears when the ThinPrep Processor detects that the door of the instrument was opened during a sequence. The instrument will automatically abort the sequence and perform error recovery.

Possible Causes

- Door opened during sequence
- System hardware malfunction

Press ENTER with door closed to retry initialization. System uninitialized.

Reason for Message

This message appears when the ThinPrep Processor detects that the door of the instrument was open during start-up of the instrument. The operator must close the door and press ENTER to retry system initialization.

Possible Causes

- Door opened during instrument start-up
- System hardware malfunction

STOP KEY PRESSED

Reason for Message

This message appears when the user presses the STOP key during a sequence. The instrument will automatically abort the sequence and perform error recovery.

Possible Causes

- STOP key pressed during a sequence

SECTION D

ERROR HISTORY

Operating errors and operator errors are logged numerically in the Error History as follows:

	Error	Minor
Vial too full. 21 ml max. allowed	3	0
Filter already wet	4	0
No fluid detected	5	0
Evacuation failure. Check filter	6	0
Waste system failure	18	0
DOOR OPEN WHILE PROCESSING SAMPLE	20	0
Sample too dense. Dilute 20:1	21	0
STOP KEY PRESSED	23	0
Press ENTER with door closed to retry initialization. System uninitialized	83	0

Chapter Five

Maintenance

SECTION A

INTRODUCTION

This chapter describes routine maintenance procedures for the ThinPrep Processor. This chapter includes the following sections:

SECTION B: Emptying Waste Bottle

SECTION C: Filter Cap Cleaning

SECTION D: Filter Cap O-ring Lubrication

SECTION E: Filter Seal O-ring Replacement

SECTION F: Door Cleaning

SECTION G: Cap Seal Cleaning

SECTION H: General Cleaning

SECTION I: Waste Tubing Replacement

SECTION J: Waste Filter Replacement

SECTION K: Moving the ThinPrep Processor

SECTION L: Maintenance Schedule

Note: Any procedure not described in this section requires specially trained personnel. Contact Cytyc Technical Service for more information.

SECTION B

EMPTYING WASTE BOTTLE

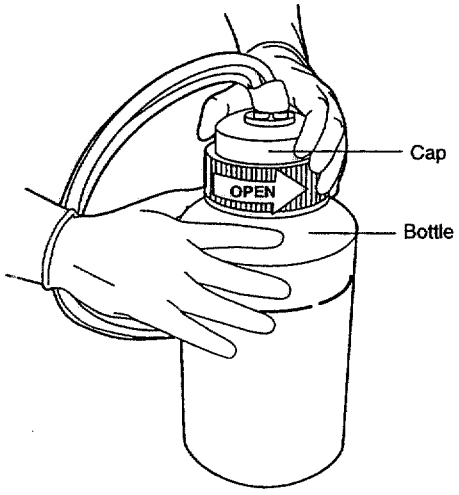
Check the waste bottle on a daily basis and empty it before the fluid level reaches the "MAX" marking on the bottle.

1. **Disable the waste system –**
   - From the Main Menu, select the down arrow key to display the second Main Menu screen.
   - Select option 7, **Maintenance.**
   - Select option 2, **Waste System.**
   - Remove all the disposables from instrument and press ENTER.
   - Wait for the system to vent the waste bottle and display the "ENTER when finished." message.
2. **Cap removal** – Open the waste bottle cap by rotating the waste cap while holding the bottle in place to avoid tangling the waste tubing.

   See Figure 5-1

   Do not remove the length of tubing connected to the inside of cap.

Figure 5-1 Opening/Closing the Waste Bottle



3. **Bleaching the waste bottle** (OPTIONAL) – The contents of the waste bottle (PreservCyt Solution) are categorized as chemical medical waste; however, bleach may be used to decontaminate the waste if desired.

WARNING: PreservCyt Solution contains a concentration of methanol and [illegible] are [illegible] and [illegible] in this formulation. PreservCyt Solution has been shown to cause greater than 99.999% per minute reduction within 30 minutes for the following microbes and viruses: *Candida albicans*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Mycobacteria tuberculosis*, Rabbitpox, Human immunodeficiency virus (HIV).

WARNING: Extreme care must be taken if bleaching the waste bottle because equipment failures may result if incorrectly performed. The waste bottle should never contain bleach when it is connected to the ThinPrep Processor. Prior to waste disposal, and after disconnecting the waste bottle cap from the waste bottle, add the desired amount of bleach to the bottle. After disposal, rinse the bottle with water to remove any remnants of bleach and then attach the bleach-free bottle to the cap assembly.

4. **Transport cover** – An extra plain cap without tubing fittings is included with the ThinPrep Processor for transporting the waste bottle. Place this cover on the waste bottle when transporting to the disposal area.

5. **Waste disposal** – Dispose of waste according to guidelines for chemically hazardous materials. PreservCyt Solution contains methanol. See Chapter 7, *Cytyc PreservCyt Solution*, for more information about PreservCyt Solution.

6. **O-ring seal** – Inspect the O-ring seal located on the inside of the waste cap assembly for any debris. If required, clean the seal with water using a lint-free wipe and apply a thin layer of lubricant grease to the o-ring from the tube included with the ThinPrep Processor.

7. **Cap replacement** – Replace the waste cap onto the bottle being careful not to pinch the tubing located on the inside of the waste cap assembly.

8. **Inspection** – Make sure the waste cap is firmly tightened. The waste cap must be tight for proper waste bottle operation.

   Check that the waste tubing between the waste bottle assembly and the ThinPrep Processor is not pinched or twisted.

   Check that the quick disconnect fittings located at the rear of the ThinPrep Processor are secure. See Chapter 2, *Installation and Specifications,* for details.

9. **Completion** – Press the ENTER key when this operation is complete. The system will be available for sample processing when the display returns to the Main Menu.

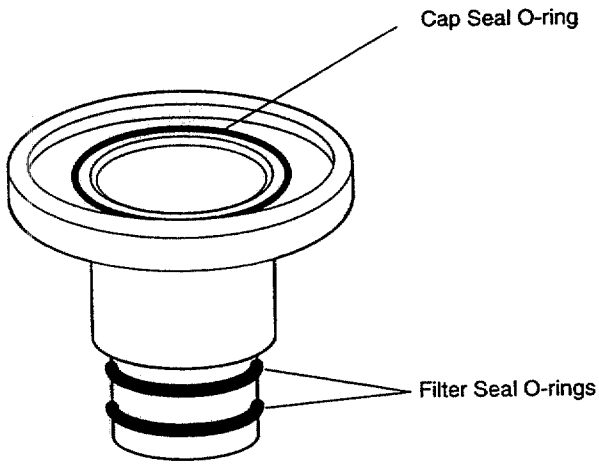
SECTION C

FILTER CAP CLEANING

Clean the filter cap daily. It is important that the top surface of the filter cap and the cap seal O-ring are free of debris for proper operation of the system.

Wipe the entire filter cap with a lint-free wipe dampened with de-ionized or distilled water to remove deposits. Dry the filter cap after cleaning.

Figure 5-2 Filter cap



SECTION D

FILTER CAP O-RING LUBRICATION

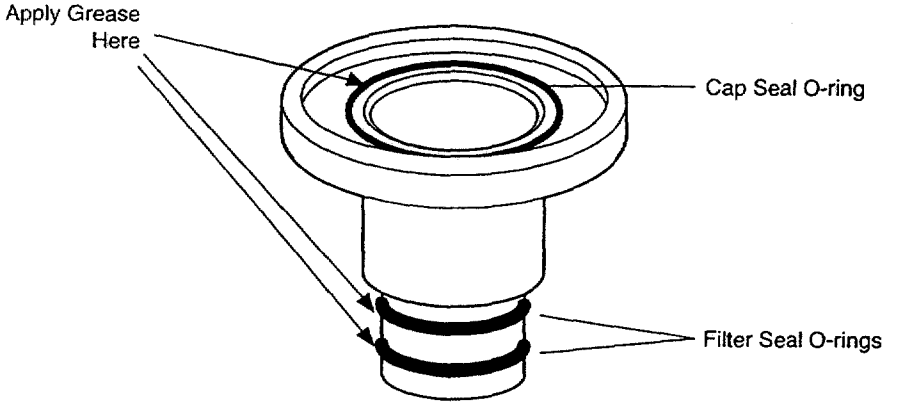
Inspect the filter seal O-rings located at the base of the filter cap for dryness. An indication of dryness is difficulty inserting a TransCyt Filter onto the filter cap.

Inspect the cap seal O-ring located at the top of the filter cap for dryness. If the cap seal O-ring is damaged, replace the entire filter cap.

Perform the following procedure weekly on the cap seal O-ring and whenever any of the filter seal O-rings are dry.

1. Using the tube of lubricant grease included with the ThinPrep Processor, apply a small amount of grease to each of the three O-rings as shown in Figure 5-3.
2. Using a gloved finger, spread the grease until a thin layer of grease covers each of the O-rings. Remove any excess grease from the three O-rings with a lint-free wipe.

Figure 5-3 Filter cap O-ring lubrication



SECTION E

FILTER SEAL O-RING REPLACEMENT

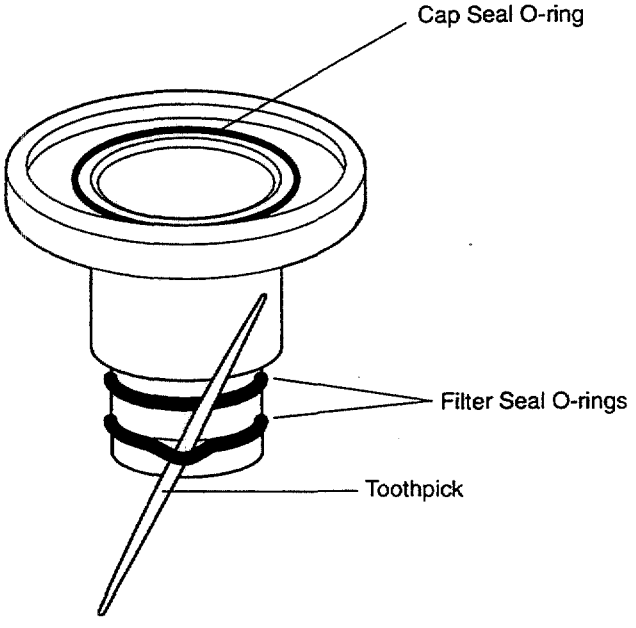
Inspect the filter seal O-rings located at the base of the filter cap for cracking or tearing. Perform the following procedure if the O-rings are cracked or torn.

If the cap seal O-ring is cracked or torn, replace the entire filter cap.

Do not attempt to remove the cap seal O-ring.

1. Using a plastic or wooden utensil (toothpick is ideal), lift filter seal O-ring out of groove then roll the O-ring off the edge of the filter cap base as in Figure 5-4.

Figure 5-4 Filter seal O-ring replacement



2. Roll the new O-ring over the edge of the filter cap base until it is seated in the appropriate groove.

3. Make sure that the new filter seal O-ring is seated properly and not twisted. Lubricate the new filter seal O-ring as described in Section D.

Note: Do not use the filter cap with only one filter seal O-ring installed. This may cause splashing during the dispersion phase and produce an insufficient seal for proper operation.

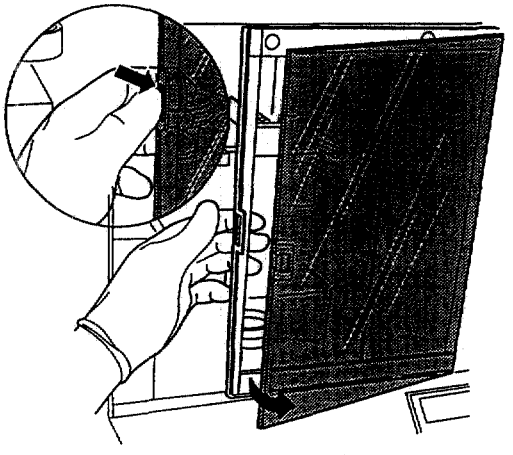
SECTION F

DOOR CLEANING

The door of the ThinPrep Processor may become dirty over time. To clean the door, it is best to use a commercially available glass cleaner.

1. It is necessary to open the door mechanism to clean the inside surface of the plastic. Slide the door open approximately three inches. With your left thumb, release the tab on the open edge of the door and push the back of the window out with your fingers. Refer to Figure 5-5.

Figure 5-5 Opening door for cleaning



2. Open the window to the right and clean the inside surface of the window.
3. Gently close the window until it snaps back into the door frame.
4. Clean the outside surface of the door's window.
5. Close the door by sliding it to the left.

SECTION G

CAP SEAL CLEANING

The cap seal is a stainless steel part that covers the top of the filter cap during sample processing. The cap seal has two tubing connections on its top side. Debris can accumulate and dry on the underside of the cap seal; therefore, periodic cleaning is required.

To clean the underside of the cap seal follow the instructions outlined below:

- From the Main Menu, select the down arrow key to display the second Main Menu screen.
- Select option 7, **Maintenance**.
- Select option 2, **Waste System**.
- Remove all the disposables from the instrument and press ENTER.
- Wait for the system to complete its movements and display the "ENTER when finished." message.

This procedure inverts the rotating plate allowing a clear view of the underside of the cap seal.

Use a lint-free wipe dampened with de-ionized water to clean any dust, dried salts, etc. from the underside of the cap seal. Upon completion of the cleaning, press the ENTER key to return to the Main Menu.

This procedure should be performed on a daily basis.

SECTION H

GENERAL CLEANING

Use a lint-free wipe, dampened with de-ionized water, to clean any dust from the filter cap bobbins, slide holder, and cabinet exterior. Turn off the power to the instrument before cleaning any areas except for the cap seal and below the sample holder.

Occasionally drops may fall off of a filter as it rotates for evacuation. These drops accumulate and dry in an area below the sample holder. This area also requires periodic cleaning. To gain access to this area, execute the Waste System sequence as described in Section G: CAP SEAL CLEANING.

In general, be sure to clean up spills when they occur. Use a lint-free wipe to absorb any spills and then wipe the area of the spill with a lint-free wipe dampened with de-ionized water.

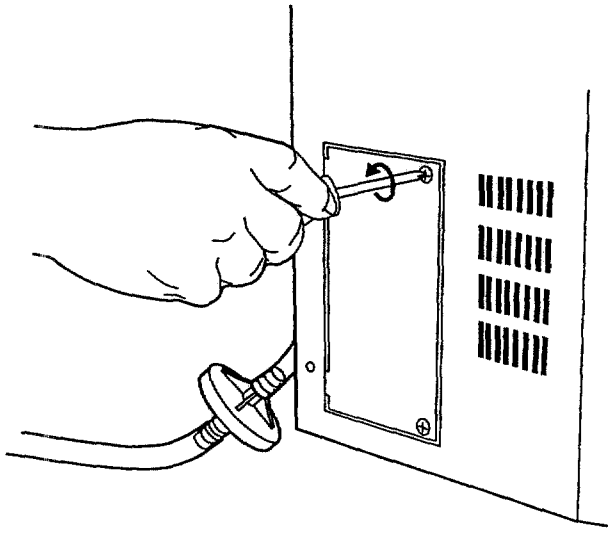
SECTION 1

WASTE TUBING REPLACEMENT

The tubing located inside the waste control box must be replaced every six months. The waste control box is accessible through the access panel located on the left side of the ThinPrep Processor.

1. Disable the waste system –
   - From the Main Menu, select the down arrow key to display the second Main Menu screen.
   - Select option 7, **Maintenance**.
   - Select option 2, **Waste System**.
   - Remove all the disposables from the instrument and press ENTER.
   - Wait for the system to complete its movements and display the "ENTER when finished." message.
2. Using the #1 tip (small) Phillips head screwdriver provided, loosen the two Phillips head screws that secure the access panel shown in Figure 5-6. Only a ¼ turn counterclockwise is required to loosen these screws. Do not attempt to unscrew them completely.

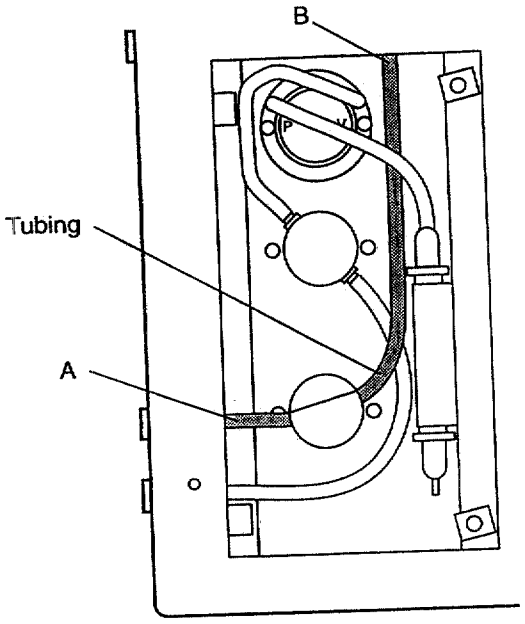
Figure 5-6



3. Remove the access panel and set it aside.

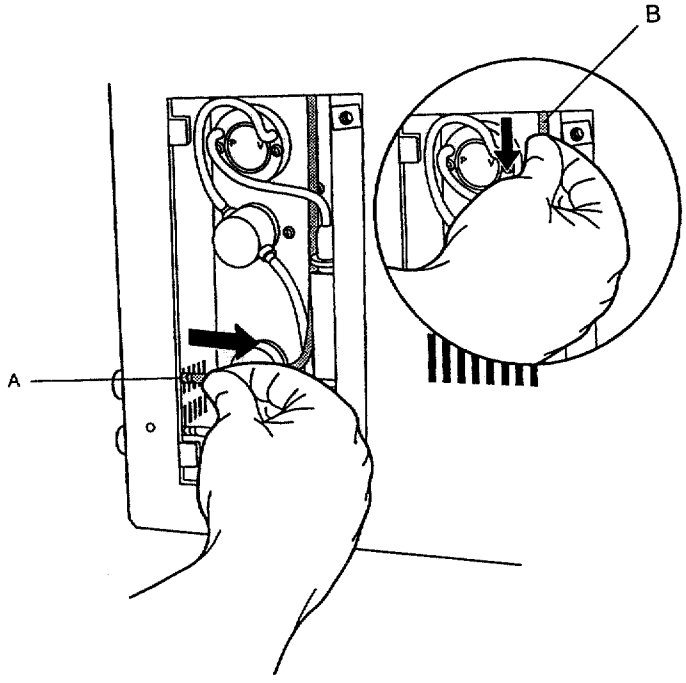
4. Locate the pieces of flexible tubing shown in Figure 5-7.

Figure 5-7



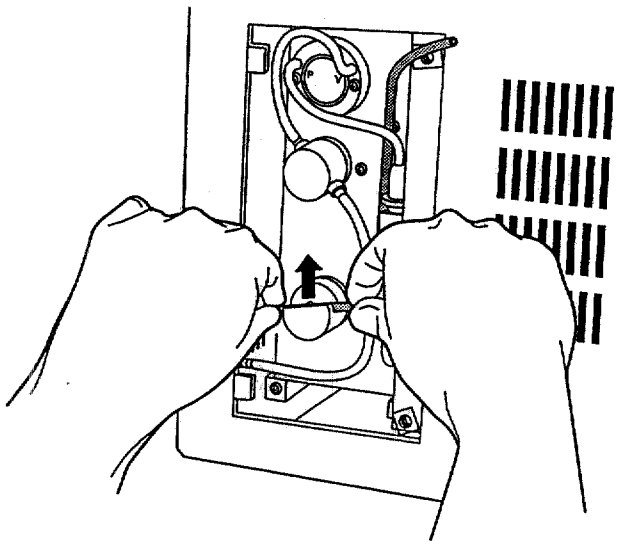
5. Detach tubing from points A and B shown in Figure 5-8.

Figure 5-8



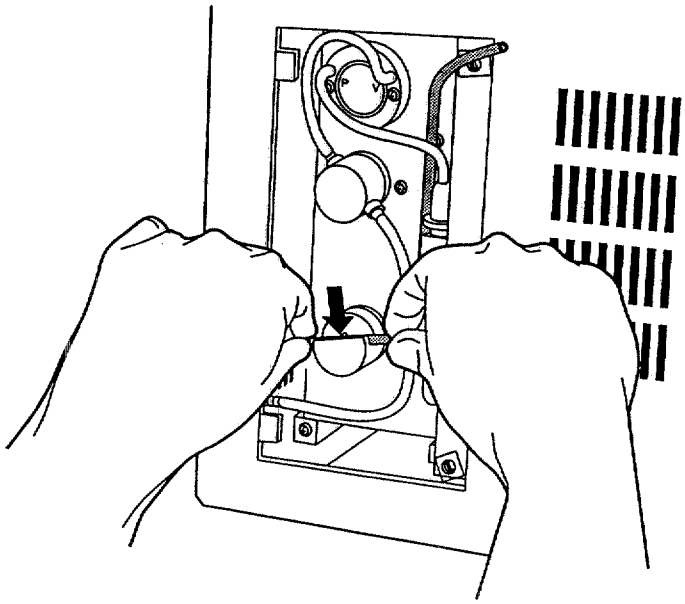
6. Holding the tubing on each side of the valve, slide it out of the valve in the direction shown in Figure 5-9. Discard tubing.

Figure 5-9



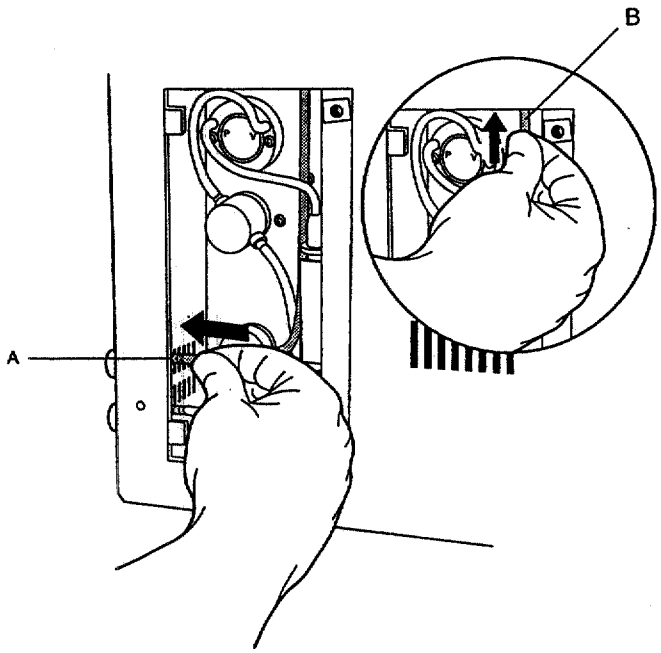
7. Locate the replacement tubing. Slide the tubing into the valve using a back and forth motion while pushing the tubing into the valve. See Figure 5-10. Make sure tubing is fully inserted and not twisted.

Figure 5-10



8. Connect the replacement tubing to points A and B shown in Figure 5-11. Make sure tubing fully covers each fitting.

Figure 5-11



9. Replace access panel and secure with the two Phillips head screws. Turn the two screws clockwise to tighten.
10. Press the ENTER key. The waste system maintenance will automatically reset and return the instrument to the Main Menu.
11. To test the new tubing installation, run a blank PreservCyt Solution sample vial (no cells) using the "Run Blank Sample" procedure outlined in Chapter 2, *Installation and Specifications*, of this manual.
12. **Note:** Additional replacement tubing is available from Cytyc.

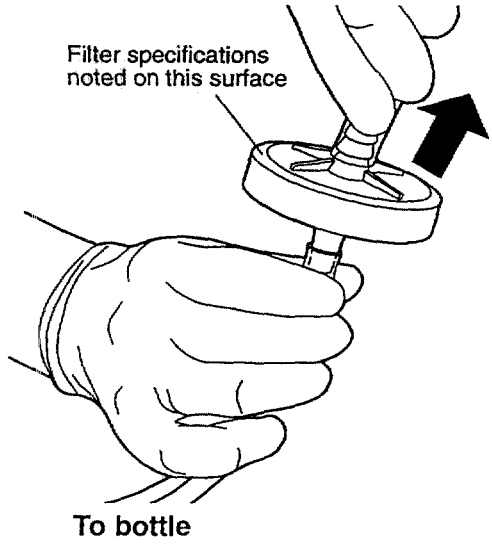
SECTION 1

WASTE FILTER REPLACEMENT

If the waste bottle is allowed to overfill, the waste filter may become wet. The ThinPrep Processor will detect a problem and report an error message.

1. Turn off the instrument.
2. Attempt to salvage the waste filter by draining the fluid from the waste filter. In the rear of the instrument, detach the bottom connector which has the waste filter in line. The liquid in the waste filter may adequately drain from the waste filter at this time. Before replacing the waste filter, reattach the connector, turn on the power, and attempt to run a blank (PreservCyt Solution vial) on the system to test its operation.
3. If the processor continues to detect a problem, turn off the power and detach all the waste connectors from the rear of the instrument.
4. Remove the tubing and connector attached to the top of the waste filter by pulling on the tubing. It may be necessary to cut the tubing. Refer to Figure 5-12.

Figure 5-12 Waste filter replacement



5. Remove the waste filter from the lower piece of tubing. It may be necessary to cut the tubing.
6. Attach the new waste filter to the lower piece of tubing.

   Make sure the new waste filter is correctly oriented. The filter specification notations on the waste filter must be on the connector side of the filter, not the waste bottle side.
7. Attach the tubing to the top of the new waste filter.
8. Reattach all the waste connectors to the rear of the instrument. Refer to Chapter 2 for more information.
9. Turn on instrument power.
10. Run a blank (PreservCyt Solution vial with no cells) on the processor to test the operation of the system.

SECTION K

MOVING THE THINPREP PROCESSOR

If it becomes necessary to change the location of your ThinPrep Processor, be sure to follow one of the two procedures described below.

Unit moved within building:

1. Turn off power.
2. Disconnect power cord from the electrical outlet and instrument.
3. Empty the waste bottle.
4. Disconnect waste bottle from the instrument at connector fittings.
5. With the help of another person, hold the instrument level and carefully place the ThinPrep Processor onto the flat surface of a cart. Roll the unit to its new location.
6. With the help of another person, lift the unit from the cart and place it onto its new surface.
7. Reconnect the power cord and waste bottle.
8. Run a blank (PreservCyt Solution vial with no cells). Refer to the instructions in Chapter 2, Section I.

Unit shipped to new location:

1. Turn off power.
2. Remove Program Memory Card by pushing in the black button.
3. Disconnect power cord from the electrical outlet and instrument.
4. Empty the waste bottle.
5. Disconnect waste bottle from the instrument at connector fittings.
6. Reattach internal securements. Refer to Chapter 2, Section D.

7. With the help of another person, hold the instrument level and carefully place the ThinPrep Processor into its box. Place the instrument's accessories in the box. Seal the box and ship the unit.

8. When the unit arrives at its destination, follow the instructions in Chapter 2, *Installation and Specifications,* for unpacking the instrument.

9. Run a blank (PreservCyt Solution vial with no cells).

SECTION L

MAINTENANCE SCHEDULE

Table 5-1 Maintenance Schedule

PROCEDURE	FREQUENCY
Waste Bottle Emptying	As needed
Filter Cap Cleaning	Daily
Pneumatic System Test (see Chapter 3)	Weekly
Cap Seal O-ring lubrication	Weekly (or as needed)
Filter Seal O-ring lubrication	As needed
Filter Seal O-ring Replacement	As needed
Door Cleaning	As needed
General Cleaning	Monthly
Waste Tubing Replacement (in pinch valve)	Six months
Waste Filter Replacement	As needed
Cap Seal Cleaning	Daily

Chapter Six

Fixation and Staining

SECTION A

INTRODUCTION

There is wide variation among laboratories in fixation, staining and coverslipping methods employed for cytologic specimens. The thin layer characteristics of ThinPrep Processor prepared slides allow precise assessment of the effects of these differences in protocols and allows the laboratory personnel to optimize their methods by following the general guidelines provided in this section. These guidelines are recommendations and should not be considered absolute requirements.

Following is a description of these ***recommended guidelines*** for fixation procedures, staining protocols and coverslipping methods.

SECTION B

FIXATION

The ThinPrep Processor deposits completed slides into a fixative bath vial that contains standard laboratory fixative alcohol. Use the following procedure to fix ThinPrep slide preparations.

1. Remove each slide after it is deposited into the fixative bath vial in the ThinPrep Processor.
2. Place the slide into a separate multi-slide holder containing standard laboratory fixative alcohol. In order to minimize exposure of ThinPrep slides to air:
   - when transferring ThinPrep slides from the fixative bath vial to the multi-slide fixative container, care should be taken to perform this operation quickly.
   - if ThinPrep slides are being transferred to a staining rack, care should be taken that ThinPrep slides are continuously immersed in fixative.
3. ThinPrep slides should be fixed for at least 10 minutes prior to staining.
4. If the ThinPrep slide will be stored dry and unstained, spray the slide with a spray fixative upon removal from the fixative bath vial. Follow spray fixative manufacturer's recommended procedure for spray fixation.

SECTION C

STAINING

General guidelines to consider when staining ThinPrep slides are:

- Staining times may be different and may require adjustment for ThinPrep slides compared to conventional preparations.
- The use of graded concentrations of alcohol in the staining process will minimize cell distortion and possible cell shedding.
- The use of mild bluing solutions and dilute acid baths will optimize nuclear staining and minimize possible cell shedding.

STAINING PROTOCOL:

A recommended staining protocol for ThinPrep slides is attached. This protocol incorporates the general staining guidelines stated above and the following specific recommendations:

1. If slides have been spray fixed, remove the spray fixative by soaking in a standard laboratory fixative for at least 10 minutes.
2. Stain the ThinPrep slides with standard modified Papanicolaou stains according to the manufacturer's routine procedures adjusting to the general guidelines for ThinPrep slide staining stated above.
3. Standard staining times for ThinPrep slides may be different from conventional slides, and it may be necessary to increase or decrease these times. It is recommended that staining times be optimized following laboratory standard operating procedures. These differences may necessitate staining ThinPrep and conventional slides separately.

174

4. Cytyc recommends minimizing exposure of slides to strong acidic or strong basic solutions since this may result in possible cell shedding. Below are recommended maximum concentrations of some solutions:

• Hydrochloric acid (HCl)	0.025%
• Lithium Carbonate (bluing) baths	10mg per liter[1]
• Acetic acid	0.1%
• Ammonium Hydroxide	0.1%

5. Avoid the use of strong salt solutions like Scotts Tap Water Substitute. Cytyc recommends the use of a dilute Lithium Carbonate solution or Ammonium Hydroxide solution as the bluing solution.
6. During the hydration dehydration process, use graded concentrations e.g. 50%, 70% of alcohol. This lowers the potential of osmotic shock and possible cell shedding during staining.
7. Bath solution heights should be sufficient to completely cover the slides.
8. Slides should be agitated for at least 10 dips in each bath.

[1] Refer to Bales, CE. and Durfee, GR. *Cytologic Techniques* in Koss, L, ed. *Diagnostic Cytology and its Histopathologic Basis.* 3rd Edition. Philadelphia: JB Lippincott. Vol. II: pp 1187–1260 for details

Table 6-1 Cytyc Staining Protocol

	Solution	Time
1.	70% Reagent Alcohol	1 minute with agitation
2.	50% Reagent Alcohol	1 minute with agitation
3.	Distilled H_2O (dH_2O)	1 minute with agitation
4.	Richard-Allan Hematoxylin I	30 seconds with agitation*
5.	Distilled H_2O (dH_2O)	15 seconds with agitation
6.	Distilled H_2O (dH_2O)	15 seconds with agitation
7.	Clarifier (0.025% glacial acetic acid)	30 seconds with agitation
8.	Distilled H_2O (dH_2O)	30 seconds with agitation
9.	Bluing Reagent (10mg LiCarb/1L)	30 seconds with agitation
10.	50% Reagent Alcohol	30 seconds with agitation
11.	95% Reagent Alcohol	30 seconds with agitation
12.	Richard-Allan Cytology Stain	1 minute with agitation
13.	95% Reagent Alcohol	30 seconds with agitation
14.	95% Reagent Alcohol	30 seconds with agitation
15.	100% Reagent Alcohol	30 seconds with agitation
16.	100% Reagent Alcohol	30 seconds with agitation
17.	100% Reagent Alcohol	30 seconds with agitation
18.	Xylene	1 minute with agitation
19.	Xylene	1 minute with agitation
20.	Xylene	3 minutes with agitation
21.	Mount in Permount	

Stains may be ordered from Richard-Allan Medical Industries, Inc. • 8850, M89, Box 351, Richland, MI • 49083-0351 • 1-800-253-7900. Hematoxylin I (7221), Richard-Allan Cytology Stain (7511). Permount is a trademark of Fisher Scientific Corp.

* Time may vary with stain lot or age.

176

SECTION D

COVERSLIPPING

The use of Permount mounting media has been evaluated and is recommended for use with ThinPrep slides by Cytyc. Since some mounting media cause 'floating' of cells to occur on ThinPrep or conventional slides, each laboratory should evaluate their choice of mounting media to insure compatibility with ThinPrep slides.

Cytyc recommends the use of 24mm × 30mm coverslips.

Other approved mounting media

- Baxter ACCU-MOUNT 60
- Shandon Clearium

SECTION E

REFERENCES

Bales, CE. and Durfee, GR. *Cytologic Techniques* in Koss, L, ed. *Diagnostic Cytology and its Histopathologic Basis.* 3rd Edition. Philadelphia: JB Lippincott. Vol. II:

178

Chapter Seven

CYTYC PreservCyt Solution

SECTION A

INTRODUCTION

The following sections describe the function and specifications of the cytologic preservative fluid, PreservCyt Solution.

SECTION B

PRESERVCYT SOLUTION

PreservCyt Solution is a methanol-based, buffered preservative solution designed to support cells during transport and slide preparation of the ThinPrep Processor.

The ThinPrep Processor slide preparation process also requires PreservCyt Solution for transporting and storing samples prior to processing. PreservCyt Solution is optimized for the ThinPrep Processor slide preparation process and cannot be substituted with any other reagents.

Packaging

Please refer to the **Purchasing Information** portion of Section 3 of the ThinPrep 2000 Operators Manual for part numbers and detailed information regarding the ordering of solutions and supplies for the ThinPrep 2000 System.

- Vials of PreservCyt Solution are contained in each ThinPrep Pap Test.

Composition

PreservCyt Solution contains methanol and buffer. It contains no reactive ingredients.

WARNING: PreservCyt Solution contains methanol. Danger. Poison. Vapor harmful. May be fatal or cause blindness if swallowed. Cannot be made non-poisonous. Keep away from fire, heat, sparks, and flame. Other solutions cannot be substituted for PreservCyt Solution.

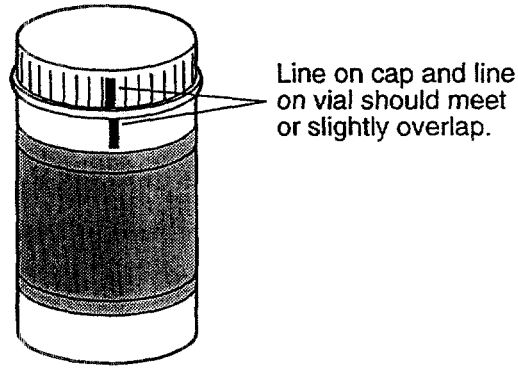
Storage Requirements

- Store the vials at 15°– 30°C (59°–86°F) without cells.
- According to the *1910 OSHA Guide*, PreservCyt Solution is a Class IC liquid and up to 120 gallons may be stored outside of an inside storage room or storage cabinet in a building or in any one fire area of a building. PreservCyt Solution must be stored in its original, DOT approved, packaging to meet this criterion.
- Once the vials contain samples, cells are preserved for approximately 3 weeks at 4°– 37°C (39°– 98.6°F).

Transportation

When transporting a PreservCyt Solution vial containing cells, make sure the vial is tightly sealed. Align the mark on the cap with the mark on the vial to prevent leakage as shown in Figure 7-1

Figure 7-1 Aligning the vial cap



The shipping category for PreservCyt Solution is "Alcohol NOS". The shipping category for PreservCyt Solution containing cells is "diagnostic sample".

Stability

Do not use PreservCyt Solution after the expiration date on the container label. If making multiple slides from the same sample vial, be sure to make the slides before the expiration date marked on the sample vial. Expired vials should be discarded using appropriate laboratory procedures. Also, refer to storage requirements above for cell preservation limits.

Handling/Disposal

Handle all chemical-containing materials carefully in accordance with safe laboratory practices. When required by reagent composition, additional precautions are marked on the reagent containers.

Dispose of PreservCyt Solution according to the guidelines for disposing of chemically hazardous materials. PreservCyt Solution contains methanol.

WARNING: PreservCyt Solution contains a concentration of methanol and alcohol which are anti-microbial and anti-viral in this formulation. PreservCyt Solution has been shown to cause greater than 99.999 percent inactivation within 15 minutes for the following microbes and viruses: Candida albicans, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Mycobacteria tuberculosis, Rabbitpox, Human immunodeficiency virus.

Interfering Substances

The use of lubricants (e.g. KY Jelly) should be minimized prior to specimen collection. Lubricants can adhere to the filter membrane and may cause poor cell transfer to the slide.

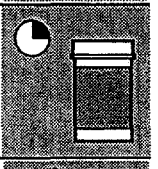
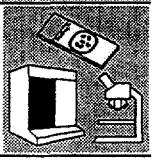
Chapter Eight

Gynecologic Sample Preparation

SECTION A

GYNECOLOGIC SAMPLES

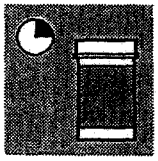
Includes cell samples from the ectocervix and the endocervix.

❶ **Collection:** Deposit the specimen directly into a PreservCyt Solution Vial.	
❷ **Allow to Stand in PreservCyt Solution for 15 Minutes**	
❸ **Run on ThinPrep Processor using Sequence 4, Fix, Stain, and Evaluate**	

SECTION
B

Allow To Stand In PreservCyt Solution For 15 Minutes

After sample transfer to the PreservCyt Solution Vial, the sample should stand for at least 15 minutes before processing.

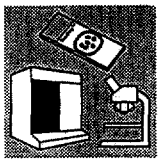


WARNING: PreservCyt Solution contains a concentration of methanol and a pH which are anti-microbial and anti-viral in this formulation. PreservCyt Solution has been shown to cause greater than 99.999 percent inactivation within 15 minutes for the following microbes and viruses: Candida albicans, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Mycobacteria tuberculosis, Rabbitpox, Human immunodeficiency virus.

For more information on PreservCyt Solution, refer to Chapter 7, *Cytyc PreservCyt Solution.*

SECTION C

Run on ThinPrep Processor Using Sequence 4, Fix, Stain, and Evaluate



The operator loads the instrument and selects the appropriate sequence number for the sample to be processed as described in Chapter 3, *Operating Instructions.* At the completion of the process, the operator fixes and stains the slide according to the procedure in Chapter 6, *Fixation and Staining.*

Chapter Nine

ThinPrep 2000 System Customer Training Program

Objective

This program provides training in the use of the ThinPrep 2000 System and training in the examination of cervical cytology ThinPrep slides. Training involves a series of glass-slide modules in which each participant will learn how to screen for and recognize a spectrum of normal and abnormal cytologic morphology on ThinPrep samples. Additionally, methods for determining specimen adequacy will be described. Conventional Pap smear preparations will be used to compare similarities and differences between the two preparation methods. At the conclusion of the training program, the participants will have attained the skills necessary to understand the morphologic presentation of ThinPrep cervical cytology slide preparations. These individuals will, in turn, be responsible for the training of their Cytopathology staff.

Training Design

Cytyc Corporation's cervical cytology training program is designed to provide training in the morphologic similarities and differences between ThinPrep sample preparations and the conventional Pap smear. The training design is based on a cumulative learning process; ThinPrep training requires retention and application of the basic fundamentals and knowledge acquired during the training period. A systematic approach is utilized with frequent assessment of the individuals' understanding of the ThinPrep principles. The training program incorporates both pre and post tests in order to assess the progress of learning.

The first phase of training is conducted by Cytyc Corporation for two individuals (cytotechnologist and pathologist) from each participating laboratory. These individuals will be responsible for training the remainder of their staff cytotechnologists and pathologists within their laboratory.

Pre-Training

Prior to training, all participants receive a copy of the *ThinPrep Morphology Reference Manual.* This illustrates the major diagnostic categories of The Bethesda System, as they appear on ThinPrep slides. Participants are asked to review the manual in advance of the training program.

Session 1

Training begins with the ThinPrep morphology lecture which is designed to familiarize the participants with the microscopic presentation of cervical samples prepared using the ThinPrep 2000 System. The format summarizes the morphologic features common to specific diagnostic entities described in The Bethesda System. ThinPrep morphology will be illustrated with transparencies and then a demonstration session at a multi-head microscope. Morphologic similarities and differences between conventional preparations and ThinPrep slides will be emphasized.

Following this introductory lecture session, a set of known (labeled) ThinPrep slides (**Evaluation Module I**) will be screened individually by all participants. The slides will contain a wide variety of diseases and disease states, including but not limited to, negative, infectious agents, intraepithelial lesions and carcinomas. Evaluation I slides will be screened by each individual as known (labeled) examples. This set of slides provides the participant a reference to the presentation of the diagnostic categories encountered. Slides are labeled with the final diagnosis allowing the screener to establish an expected range of cytologic presentation. Specimen adequacy (Endocervical Component specifically) for each slide is presented as an unknown as part of the training. Following this individual review session, slides will be reviewed with a Cytyc staff cytotechnologist in a group setting employing a multi-head microscope.

Session 2

A set of unknown ThinPrep cervical cytology slides is used to test the baseline competency of each participant (**Test 1**). Each participant will be required to screen and diagnose this initial set of slides. Slides are unmarked which allows an evaluation of screening (locator) and interpretive skills. Participants are given a timed exam period and answer sheet that has been designed following current CLIA guidelines. Specimen adequacy (Endocervical Component specifically) and

diagnostic interpretation for each slide is assessed as part of this exam. The slides and correct responses are reviewed individually by each participant at their own microscope and then in a group session using a multi-head microscope format directed by a Cytyc staff cytotechnologist.

Following Test 1, a set of unknown ThinPrep slides (**Evaluation Module II**) is screened individually by all participants. These slides contain a wide variety of diseases and disease states, including but not limited to, negative, infectious agents, intraepithelial lesions and carcinomas. After the initial slide examination, participants will be given the answers to Evaluation II and will review these slides at their own microscopes. A final discussion of these cases at a multi-head microscope will be led by the Cytyc staff cytotechnologist.

Session 3

A Cytyc staff cytotechnologist will conduct a review session with all participants employing a **Self-Study Module** of known ThinPrep slides. This session will be used to summarize the morphologic findings inherent to the ThinPrep slide preparations. An emphasis will be placed on the diagnostic entities participants had difficulties with in the previous training modules. Slide sets are arranged to easily compare diagnostic entities which may resemble each other morphologically (look-a-likes).

Following this Self-Study review session a set of unknown ThinPrep slides (**Evaluation Module III**) will be screened individually by all participants. These slides will contain a wide variety of diseases and disease states, including but not limited to, negative, infectious agents, intraepithelial lesions and carcinomas. Following this individual screening, participants will be given the answers to Evaluation III and will review these slides at their own microscopes. A final discussion of these cases at a multi-head microscope will be led by a Cytyc staff cytotechnologist.

Upon completion of Evaluation Module III a series of Implementation lectures are given to prepare the participants for the training to be conducted in their individual laboratories. Training will include the cytopreparation support staff and Ob-Gyn Clinicians and Nurse Practitioners as well as the cytopreparation staff. Materials are distributed and explained.

Session 4

A final competency test consisting of a set of unknown ThinPrep slides (Test 2) will be administered to test ThinPrep screening and interpretive skills of each participant. This final exam will be modeled after current CLIA guidelines. Participants are given a timed exam period and an answer sheet following current CLIA guidelines. Both diagnostic interpretation and determination of specimen adequacy (Endocervical Component specifically) for each slide is assessed in this examination. Following administration of Test 2, the slides and correct responses are reviewed individually by each participant at their own microscope and then in a group session using a multi-head microscope format directed by a Cytyc staff cytotechnologist. CLIA Proficiency Test Program standards will be used as guidelines in establishing pass / fail scoring criteria. Individuals who pass Test 2 (90% or better) are qualified to begin training cytotechnologists and pathologists in their laboratory and the Implementation Split-Sample Analysis in their respective laboratories under the supervision of the Technical Supervisor.

Training Program participants who fail Test 2 (< 90%) will require remedial training in their individual laboratories prior to the start of their Cytopathology Staff Training. Remedial training will be conducted by a Cytyc Cytology Applications Specialist using study sets provided by Cytyc Corporation and require a Test score of 90% or better for re-entry into the training process.

Laboratory Training

Following successful completion of the Cytology Training Program, participants will be equipped with materials that will facilitate the training process within their laboratory. The Technical Supervisor of each laboratory is responsible for overseeing the morphology training and a split-sample evaluation. Morphology training within the laboratory mimics the Cytology Training Program established by Cytyc Corporation (see above). After successful completion of the morphology training, a split-sample evaluation is conducted. The split-sample evaluation, the **Implementation Split-sample Screening Analysis** (ISSA), will involve collection of split samples, preparation of matched pairs (conventional and ThinPrep slides) and examination of the

matched slide pairs by laboratory personnel. This process will continue until the Technical Supervisor of the laboratory determines that an individual is qualified to screen ThinPrep slides. In addition, the Technical Supervisor of each laboratory will be provided with materials necessary to adequately prepare and train specimen collectors including physicians, nurse practitioners and physician assistants. The Technical Supervisor will be responsible for ensuring adequate training of those individuals prior to the use of the ThinPrep System.

190

INDEX

INDEX

INDEX

INDEX

194