# Class II Special Controls Guidance Document: Premarket Notifications for Automated Differential Cell Counters for Immature or Abnormal Blood Cells; Final Guidance for Industry and FDA

**Document issued on: December 4, 2001**

This document supersedes Guidance for Premarket Notifications for Automated Differential Cell Counters for Immature or Abnormal Blood Cells; Final Guidance for Industry and FDA, November 1, 2000


**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Devices and Radiological Health**

**Hematology and Cytology Devices Branch**
**Division of Clinical Laboratory Devices**
**Office of Device Evaluation**

# Preface

## Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

For questions regarding the use or interpretation of this guidance contact Larry J. Brindza at 301-594-1293 or email ljb@cdrh.fda.gov.

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# Table of Contents

# Class II Special Controls Guidance Document: Premarket Notifications for Automated Differential Cell Counters for Immature or Abnormal Blood Cells; Final Guidance for Industry and FDA

***This document is intended to provide guidance. It represents the Agency's current thinking on the above. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.***

## 1. Background

This guidance document was developed as a special control guidance to support the reclassification of the Automated Differential Cell Counter (ADCC) device into class II. The device, as classified, is intended to identify one or more of the formed elements of blood. These devices may also have the capability to flag, count, or classify immature or abnormal hematopoietic cells of blood, bone marrow, or other body fluids. The device may use a combination of an electronic particle counting method, an optical method, or a flow cytometric method utilizing monoclonal cluster designation (CD) markers. The device includes accessory CD markers. This guidance will be issued in conjunction with a Federal Register notice announcing reclassification of this device type.

As stated on the coversheet, this guidance supersedes **Guidance for Premarket Notifications for Automated Differential Cell Counters for Immature or** Abnormal Blood Cells; Final Guidance for Industry and FDA, **issued November 1, 2000.** We re-titled and updated the November 1, 2000 guidance to more clearly reflect that it is a Class II Special Control Guidance Document. We have not revised any of the document's recommendations about the performance characteristics or labeling for an ADCC device.

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of the ADCC device. Thus, a manufacturer who intends to market a device of this generic type must (1) conform with the general controls of the Federal Food, Drug & Cosmetic Act (the Act), including the 510(k) requirements described in 21 CFR 807 Subpart E, (2) address the specific risks to health associated with ADCC device, and unless exempt from the premarket notification requirements of the Act, (3) receive a substantial equivalence determination from FDA prior to marketing the device.

This special control guidance document identifies the classification, product code, and classification identification for the ADCC device. In addition, it lists the risks to health identified by FDA and serves as the special control that, when followed and combined with general controls, will generally address the risks associated with this generic device type and lead to a timely 510(k) review and clearance. For the specific content requirements of a 510(k) submission, you should refer to 21 CFR 807.87 and other agency documents on this topic, such as **510(k) Manual - Premarket Notification: 510(k) - Regulatory Requirements for Medical Devices**, http://www.fda.gov/cdrh/manual/510kprt1.html.

Device manufacturers may submit an Abbreviated 510(k) when: (1) a guidance document exists, (2) a special control has been established, or (3) FDA has recognized a relevant consensus standard. FDA believes an Abbreviated 510(k) is the least burdensome means of demonstrating substantial equivalence once a Class II Special Controls Guidance Document has been issued. See also **The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance**, http://www.fda.gov/cdrh/ode/parad510.html.

An Abbreviated 510(k) submission must include the required elements identified in 21 CFR 807.87, including a description of the device, the intended use of the device, and the proposed labeling for the device. An Abbreviated 510(k) should also include a summary report. In an Abbreviated 510(k), FDA may consider the contents of a summary report to be appropriate supporting data within the meaning of 21 CFR 807.87(f) or (g).

The summary report should briefly describe the methods or tests used and the acceptance criteria applied to address the risks identified in this guidance document as well as any additional risks specific to your device. When a suggested test method is followed, a simple reference to the method will be an acceptable description. If there are any deviations from a suggested test method, you should provide more detailed information in the summary report to characterize the particular deviation. The summary report should also either (1) briefly present the data resulting from each test in tabular form **or** (2) describe the acceptance criteria to be applied to the test results. (See also 21 CFR 820.30 Subpart C Design Controls for the Quality System Regulation.)

# 2. The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to comply with the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "**A Suggested Approach to Resolving Least Burdensome Issues**" document. It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html.

# 3. Scope

The scope of this document is limited to the following devices:

| | |
|---|---|
| Product Code: | GKZ |
| Classification: | Class II |
| Panel: | Hematology and Pathology Devices Panel (81) |
| Review Required: | Premarket Notification, 510(k) submission |
| Regulation: | 21 CFR 864.5220 Automated Differential Cell Counter |

The classification identification below identifies the device as it existed at the time of reclassification.

§ 864.5220 Automated Differential Cell Counter.

(a) *Identification.* An automated differential cell counter is a device used to identify one or more of the formed elements of the blood. The device may also have the capability to flag, count, or classify immature or abnormal hematopoietic cells of the blood, bone marrow, or other body fluids. These devices may combine an electronic particle counting method, optical method, or a flow cytometric method utilizing monoclonal CD (cluster designation) markers. The device includes accessory CD markers.

(b) *Classification.* Class II (special controls). The special control for this device is the FDA document "Class II Special Controls Guidance Document: Premarket Notifications for Automated Differential Cell Counters for Immature or Abnormal Blood Cells; Final Guidance for Industry and FDA."

# 4. Risks to Health

FDA has identified the following risks to health generally associated with the use of ADCC device in the table below. You should also conduct a risk analysis, prior to submitting your 510(k), to identify any other risks specific to your device. The premarket notification should describe the risk analysis method. The measures recommended to mitigate the identified risks are given in this guidance document, as shown in the table below. (If you elect to use an alternative approach to address a particular risk, or have identified risks additional to those in the guidance, you should provide sufficient detail to support the alternative approach.)

| Identified risk | Recommended mitigation measures |
|---|---|
| Error in the diagnosis of a blood cell disorder | Sections 7-15 |
| Inappropriate therapy | Sections 7-15 |

# 5. Controls

FDA believes that the controls in the following sections of this guidance, when combined with general controls, will address the identified risks to health generally associated with the use of the ADCC device. You should demonstrate that your device complies with either the specific recommendations of this guidance or with an alternate means to address the above-identified risks and to provide reasonable assurance of the safety and effectiveness of the device. If you have identified any additional risks, specific to your device, your 510(k) should identify those risks, as well as the methods or tests used and the acceptance criteria applied to address them.

# 6. Abbreviated 510(k) Content

An Abbreviated 510(k) that relies on a Class II Special Controls Guidance Document should contain the following.

### Coversheet

The coversheet should prominently identify the submission as an Abbreviated 510(k) and cite the title of the specific Class II Special Controls Guidance Document.

### Items Required Under 21 CFR 807.87

The items required under 21 CFR 807.87 are:

- Description of the device. You should describe the method or technique and provide photographs, drawings, and/or schematics sufficient to provide an overview of the technology. As examples, the device technology may include, but is not limited to the following automated methodologies: pattern recognition, optical, fluorescence, flow technology, impedance, cluster analysis, and cytochemistry. You should also include limitations of the method that result from the technology.

- Intended use of the device. You should also submit an "indications for use" enclosure. See http://www.fda.gov/cdrh/ode/indicate.html for the recommended format.
- Proposed labeling for the device.

- Summary report. The summary report should describe how the Class II Special Controls Guidance Document was used to address the risks associated with the particular device type. In an Abbreviated 510(k), FDA may consider the contents of a summary report to be appropriate supporting data within the meaning of 21 CFR 807.87(f) or (g). The summary report should contain:

    - Risk analysis.

    - Description of device performance requirements.

    - Discussion of the features and functions provided to address the risks identified in this Class II Special Controls Guidance Document, as well as any additional risks identified in your risk analysis.

    - For each performance aspect identified in sections 7-15 of this Class II Special Controls Guidance document, you should briefly discuss each test method and identify your acceptance criteria. When a suggested test method is followed, a simple reference to the method will be an acceptable description. If there are any deviations from a suggested test method, you should provide more detailed information in the summary report to characterize the particular deviation. The summary report should also either (1) briefly present the data resulting from each test in tabular form **or** (2) describe the acceptance criteria to be applied to the test results. If any test article does not meet the identified acceptance criteria, you may not market your device. Instead, you must submit a new 510(k) with revised acceptance criteria. The new 510(k) must be cleared by FDA before you market your device.

    - If any part of the device design or testing relies on a recognized standard, the summary report should include: (1) a statement that testing will be conducted and meet specified acceptance criteria before the product is marketed or (2) a declaration of conformity to the standard. Testing must be completed before submitting a declaration of conformity to a recognized standard. (21 USC 514(c)(2)(B)). For more information, see FDA guidance, **Use of Standards in Substantial Equivalence Determinations; Final Guidance for Industry and FDA**, http://www.fda.gov/cdrh/ode/guidance/1131.html.

If it is not clear how you have addressed the risks identified by FDA or by your risk analysis, we may request additional information about aspects of the device's performance characteristics.

As an alternative to submitting an Abbreviated 510(k), you can submit a traditional 510(k) that provides all of the information and data described in this guidance. A traditional 510(k) should include all of your protocols, data, acceptance criteria, data analysis, and conclusions.

# 7. Software Validation Activities

Please refer to the **Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices** (hereafter, the Software Guidance), http://www.fda.gov/cdrh/ode/software.pdf, for a discussion of the software documentation that you should provide. FDA generally considers ADCC devices to be of "moderate" level of concern for the purposes of software review.

We encourage you to take advantage of any recognized software standards and provide statements or declarations of conformity as described in FDA guidance, Use of Standards in Substantial Equivalence Determinations, already cited. Please visit the following website to search for the standards that have been recognized when a medical device contains software, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm. We have created a supplemental data sheet for each software standard that we have recognized. The supplemental data sheet includes a table that indicates the documentation that you should include in a submission when you submit a declaration of conformity.

If the device includes off-the-shelf software, you should provide the additional information as recommended in the **Guidance for Industry, FDA Reviewers and Compliance on Off-the-Shelf Software Use in Medical Devices**, http://www.fda.gov/cdrh/ode/1252.html.

# 8. Accuracy

In order to characterize the accuracy of your ADCC device, we suggest comparing each test parameter to a reference method, if available. You should follow National Committee for Clinical Laboratory Standards (NCCLS) documents:

*Reference Leukocyte Differential (Proportional) and Evaluation of Instrumental Methods, Approved Standard,* NCCLS document H20-A (ISBN 1-56238-131-8), NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 1992.

*Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline,* NCCLS document EP9-A (ISBN 1-56238-283-7), NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 1995.

# 9. Precision

To establish the precision of your device, you should follow the NCCLS document:

*Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline,* NCCLS document EP5-A (ISBN 1-56238-145-8) NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 1999.

# 10. Performance

For general guidance on how to characterize the performance of your device, you should follow the International Council for Standardization in Haematology (ICSH) document cited below.

> Guidelines for the evaluation of blood cell analyzers including those used for differential leucocyte and reticulocyte counting and cell marker applications. International Council for Standardization in Haematology: prepared by the ICSH expert panel on cytometry. *Clin Lab Haematol*, 16(2):157-174, 1994.

You should establish the performance characteristics of your device, including Clinical Sensitivity and Specificity, for normal and pathological specimens. You should follow these NCCLS documents in obtaining these data:

> *Reference Leukocyte Differential (Proportional) and Evaluation of Instrumental Methods, Approved Standard*, NCCLS document H20-A, (ISBN 1-56238-131-8), NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 1992.
>
> *Preliminary Evaluation of Quantitative Clinical Laboratory Methods, Approved Guideline*, NCCLS document EP 10-A, (ISBN 1-56238-348-5), NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 1998.
>
> *Assessment of the Clinical Accuracy of Laboratory Tests Using Receiver Operating Characteristic (ROC) Plots, Approved Guideline*, NCCLS document GPIO-A, (ISBN 1-56238-285-3), NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 1995.

Where applicable, you should state the method used to perform the test and the test characteristic obtained. You should also state the background result for the method/technology used.

# 11. Linearity

You should validate the linear range of each measured test parameter with normal and abnormal specimens. We suggest using the following criteria for linearity performance testing:

- The data should fit a linearity regression line.
- The coefficient of determination ($r^2$) should be > 0.95.
- You should use a minimum of five dilutions distributed within the linear range.
- The dilution should cover the reportable range for the test parameter.
- Each dilution result should be the mean value of duplicate measurements on the same range.

# 12. Carryover

Where applicable, you should evaluate carryover from high to low specimens. You should analyze a high specimen three consecutive times followed by a low specimen three consecutive times, following the protocol described in the ICSH document cited below.

Guidelines for the evaluation of blood cell analyzers including those used for differential leucocyte and reticulocyte counting and cell marker applications. International Council for Standardization in Haematology: prepared by the ICSH expert panel on cytometry. *Clin Lab Haematol,* 16(2):157-174, 1994.

# 13. Specimens

Where applicable, you should establish the type(s) of anticoagulants, specimen age, storage conditions, etc. that are appropriate for use with your device. You should follow the NCCLS document:

*Procedures for the Collection of Diagnostic Blood Specimens by Skin Puncture; Approved Standard--Fourth Edition,* NCCLS document H4-A4, (ISBN 1-56238-111-9), NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 1999.

You should also follow the ICSH document below, where applicable.

Recommendations of the International Council for Standardization in Haematology for ethylenediaminetetraacetic acid anticoagulation of blood for blood cell counting and sizing. *Am J Clin Path,* 100(4)371-372, 1993.

# 14. Reference Values

You should describe the approach taken to interpret the observed values. When appropriate, you should distinguish between clinical and statistical significance. You should follow the ICSH/International Federation of Clinical Chemistry (IFCC) documents:

IFCC and ICSH: Approved recommendation (1986) on the Theory of Reference Values. Part 1. The concept of reference values. *J Clin Chem Clin Biochem,* 25:337-342, 1987.

IFCC and ICSH: Approved recommendation (1987) on the Theory of Reference Values. Part 5. Statistical treatment of collected reference values. Determination of reference limits. *J Clin Chem Clin Biochem,* 25:645-656, 1987.

IFCC and ICSH: Approved recommendation (1987) on the Theory of Reference Values. Part 6. Presentation of observed values related to reference values. *J Clin Chem Clin Biochem,* 25:657-662, 1987.

You should also follow the NCCLS document:

> *How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline—Second Edition*, NCCLS document C28-A2, (ISBN P56238-269-I), NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 2000.

# 15. Labeling

The premarket notification must include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). Final labeling for an *in vitro* diagnostic device must comply with the requirements of 21 CFR 809.10 before being introduced into interstate commerce, however, final labeling is not required for 510(k) clearance. Your labeling should include the specific aspects of ADCC performance as discussed in this special controls guidance document. This includes accuracy, precision, specificity, and sensitivity, as well as any limitations of the ADCC. In order to meet the requirements of 21 CFR 809.10(b)(12), you must also summarize the test methods used to generate all performance data appearing in final labeling, as well as describe the statistical methods used in analysis. Additionally, complete instructions for use must be provided, including clinical indications for use and their significance, a discussion of any extrinsic factors or interfering substances that affect results, and the circumstances under which more sensitive or additional testing should be conducted.