



DECEMBER 2007

CELL- DYN SAPPHIRE

HEALTH TECHNOLOGY ASSESSMENT UNIT

MEDICAL DEVELOPMENT DIVISION

MINISTRY OF HEALTH MALAYSIA

021/07

Prepared by:

Dr Izzuna Mudla bt Mohamed Ghazali
Principal Assistant Director
Health Technology Assessment Unit
Ministry of Health Malaysia
December 2007

Miss Sin Lian Thye
Nursing Sister
Health Technology Assessment Unit
Ministry of Health Malaysia
December 2007

Reviewed by:

Datin Dr Rugayah bt Bakri
Deputy Director
Health Technology Assessment Unit
Ministry of Health Malaysia
December 2007

EXECUTIVE SUMMARY

Interpretation of hematology results is crucial in diagnosing and management of various diseases.

This technology review was requested by the Director General of Health, Malaysia.

The objective of this review was to assess the safety, effectiveness and cost-effectiveness of CELL-DYN Sapphire™

CELL-DYN Sapphire™ a high-end hematology analyzer utilizes patented MAPSS™ plus 3-color fluorescent technology for improved lab efficiency. It allows cell population analysis by monoclonal antibody fluorochromes analogous to flow cytometry.

CELL-DYN Sapphire™ was approved by FDA. There was limited evidence retrieved. Evaluation studies showed that CELL-DYN Sapphire™ was comparable with other hematology analyzers such as Beckman Coulter LH750 and Bayer Advia in the measurement of WBC and differentials and RBC parameters. CELL-DYN Sapphire™ able to provide additional information from monoclonal antibodies analysis to enumerate and classify abnormal leucocyte forms.

In conclusion, there was fair evidence on accuracy of CELL-DYN Sapphire™ and no evidence retrieved on safety and cost-effectiveness of the device.

1. INTRODUCTION

Haematology is the analysis of the numbers, sizes and types of blood cells in the blood stream. A correct interpretation of hematology results is essential in diagnosing, managing and monitoring of various diseases.

Hematology analyzers are the main equipments in clinical laboratory. A high-end, high-volume analyzers deliver reliable red blood cell counts, platelet counts, and 5-part differentials of white blood cells, identifying lymphocytes, monocytes, neutrophils, eosinophils, and basophils. Nucleated red blood cell counts and immature granulocytes are emerging as sixth and seventh parameters.

The first automated cell counters came out in the 1950s based on Coulter's electrical impedance principle in which cells pulled through an aperture break an electric circuit, indicating both the presence of a cell and the size of the cell. The 'prehistoric' analyzers only produced counts and indices—mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration.¹

In the 1970s, automated platelet counters, 7-parameter complete blood count (CBC) analyzers, and 3-part differential leukocyte counters (for lymphocytes, monocytes, and granulocytes) entered the market. For the first time, manual differentials were not the only way to analyze white blood cells. In the 1980s, a single instrument could produce a 10-parameter CBC. The 1990s brought further advancements in leukocyte differentials with the use of flow-cell techniques based on either electrical impedance or light scatter properties.¹

Hematology analyzers evolved toward flow cell-based technologies, where cells are interrogated cell by cell through optical systems that can measure more parameters than before.¹

CELL-DYN Sapphire™ is a high-end hematology analyser manufactured by Abbott Technologies. It allows cell population analysis by monoclonal antibody fluorochromes analogous to flow cytometry.

This technology review was requested by the Director General of Health, Ministry of Health Malaysia.

2. OBJECTIVES

To determine the safety, effectiveness and cost-effectiveness of CELL-DYN Sapphire™ a high end hematology analyzer.

3. TECHNICAL FEATURES

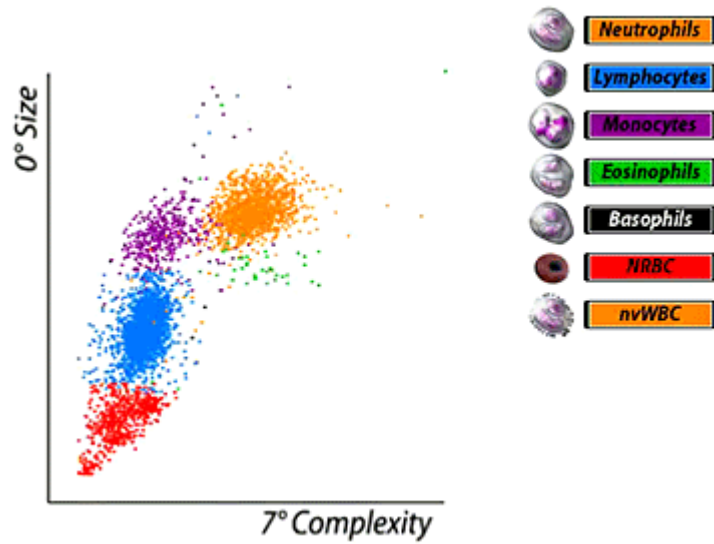


CELL-DYN Sapphire™ is an automated, high-volume hematology instrument produced by ABBOTT Laboratories that incorporates monoclonal assays and offer fluorescent staining and advanced optical platelet analysis.

According to the manufacturer the key benefits of CD-Sapphire are:²

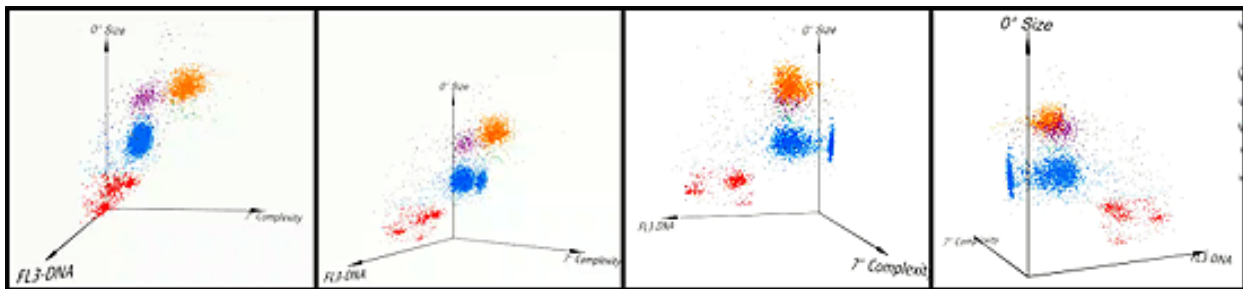
- Patented MAPSS™ *plus* 3- color fluorescent technology increases accuracy for better patient care
- First pass fluorescent NRBC analysis improves efficiency and patient care
- First pass optical platelet analysis provides greater confidence to the laboratory and physician
- Routine monoclonal analysis now allows Hematology Analyzers to be truly Diagnostic Instruments
- The internal design provides dependability, which minimizes service and maintenance requirements
- Simple, automated, single mode calibration makes calibration procedures a quick and easy operation
- Minimal maintenance with on board automated logs to track every maintenance action ensures a reliable system and increases laboratory efficiency

WBC and Differential ²



Multi-dimensional cell classification using patented Multi Angle Polarized Scatter Separation (MAPSS™) *plus* 3-color Fluorescent technology provides analysis of both the White Blood Cell count and the differential on the CELL-DYN Sapphire™. MAPSS™ *plus* 3-color Fluorescence uses fluorescent flowcytometric measurements of multiple angles of light scatter of up to 20,000 cellular events. This unique process enables multiple scatterplots to be produced to further the characterization of cellular events. Information is available on the CELL-DYN Sapphire™ to provide:

- Identification and enumeration of WBCs and subpopulations
- Identification of abnormal cell types
- Identification of interfering substances thereby giving:
 - First pass identification of NRBCs
 - Accurate Identification of Platelet Clumps

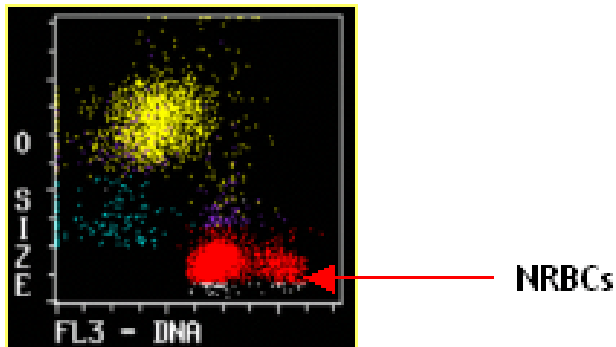


WBC differentials are virtually free of interference from NRBCs, clumped platelets, and debris providing improved laboratory efficiency and better patient care.

A Resistant RBC Mode enables samples flagged for the presence of resistant RBCs to be analyzed by a stronger lytic method to exclude resistant RBCs from the total WBC count and

differential, resulting in a reduction of manual slide reviews and manual verification of the WBC count.

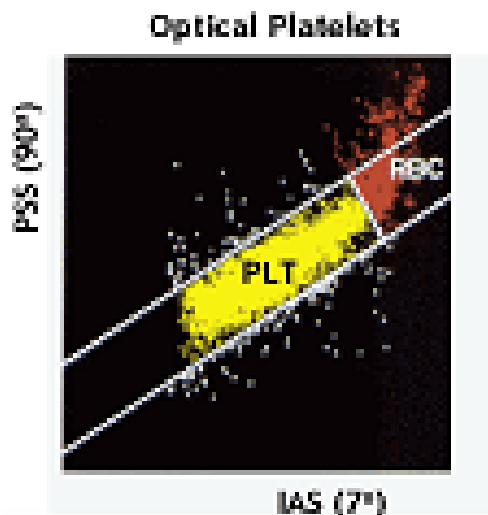
Nucleated Red Blood Cell (NRBC) Enumeration ²



Using red fluorescence, every sample is analyzed for the presence of Nucleated Red Blood Cells (NRBCs). The fluorescent DNA measurement then identifies NRBCs improving the ability to accurately detect pathology.

NRBCs, on the CELL-DYN Sapphire™ are enumerated as a unique nucleated cell sub-population, eliminating the need to correct the WBC count.

Platelet Analysis²

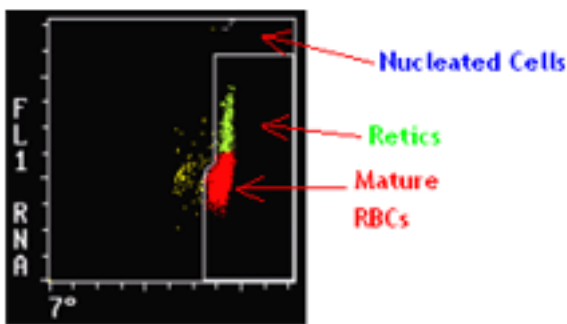


The Platelet Count is considered the one of the most clinically important CBC parameters. The CELL-DYN Sapphire™ uses multiple technologies to provide the highest degree of accuracy for this critical result.

The primary method employs the use of dual angle optical analysis, which has the ability to eliminate common interferences such as fragmented or small red blood cells. Every count is validated by an impedance method notifying the operator of possible interferences.

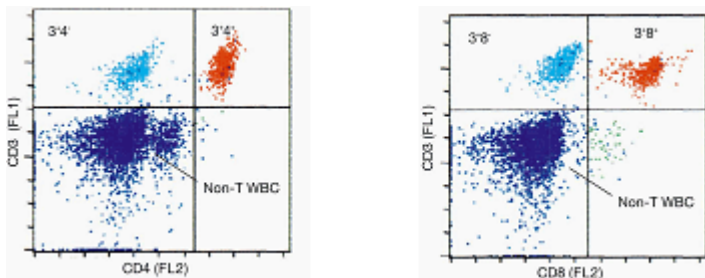
Importantly, the CELL-DYN Sapphire™ also has the unique ability to offer yet a third platelet method. The fully automated, random access CD61 monoclonal marker is specific for platelets. This optional monoclonal method can prove beneficial in verification of critical platelet results that are complicated with interferences as well as giving increased confidence in platelet transfusion management.

Reticulocyte²



The CELL-DYN Sapphire™ uses true fluorescent flow cytometry providing automated, random access reticulocyte analysis. This method allows for excellent separation of mature RBCs, platelets and the presence of leukocytosis from the reticulocyte population. The fluorescent method also provides an Immature Reticulocyte Fraction – IRF. With high sensitivity, the IRF is able to provide further clinical information when monitoring bone marrow response.

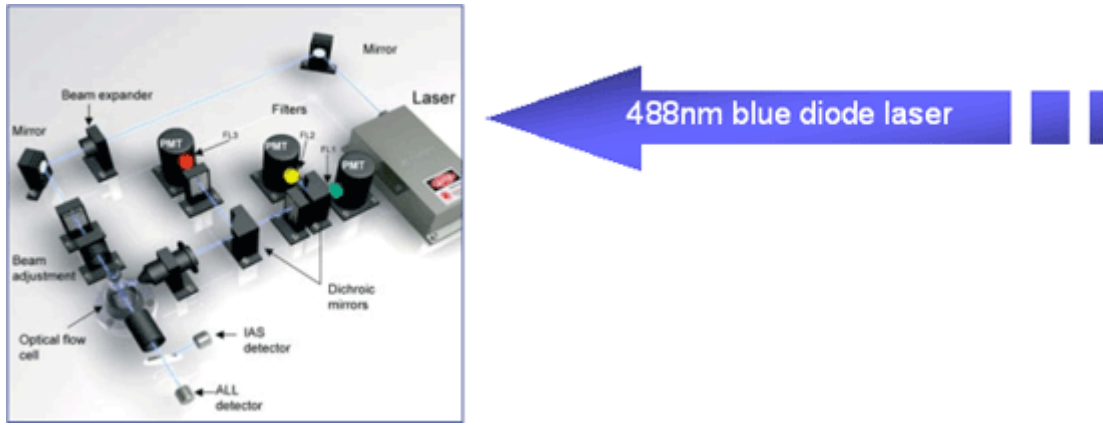
Fully Automated Monoclonal Antibody Analysis²



According to the manufacturer, CELL-DYN Sapphire™ is the only routine Hematology Analyzer that is able to provide fully automated, random access monoclonal antibody analysis. This unique ability offers the laboratory reportable, fully automated CD61 immunoplatelet count in approximately 4 minutes, and a fully automated CD3/4 and CD3/8 Immuno T-cell count is in approximately 7 minutes.

In addition, the ability to download FCS (flow cytometry standard) files opens up additional opportunities for monoclonal analysis on the CELL-DYN Sapphire™ analyzer.

CELL-DYN Sapphire™ Specifications²



- The 100 sample autoloader shares a single fluidic pathway with the open (micro) mode. This eliminates potential bias that can occur between multiple processing modes providing better confidence in patient results.
- Full data management with data storage for 10,000 cycles with intuitive software and graphics allows for easy assessment of patient results and simplified staff training.
- Onboard searchable operator's manual provides easy access to information.

4. METHODOLOGY

4.1 SEARCH METHODS

Literature were searched through electronic databases, which included Pubmed, OVID, Proquest, Ebscohost, EBM Reviews for controlled trials, Cochrane database on systematic review, Cochrane Clinical Trial Registry, Science Direct, Springer Link, and general databases such as Google and Yahoo. The manufacturer's website was also searched for relevant articles.

The search strategy used the terms, which are either used singly or in various combinations: "Cell-dyn sapphire" OR "CD sapphire", "hematology analyser" OR "haematology analyser", effectiveness OR efficacy, safety OR safe OR "adverse effect*" OR "harm* effect*" OR toxicity, "cost effectiveness" OR "cost analysis" OR econom*. There were no limitations in the search.

4.2 SELECTION OF STUDIES INCLUDED/EXCLUDED

All primary papers, systematic reviews or meta analysis pertaining to safety, effectiveness and cost effectiveness of CELL-DYN Sapphire™ were included in this study.

A critical appraisal of all relevant literature was performed and the evidence level graded according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001) (Appendix 1).

5. RESULTS AND DISCUSSION

There were few evidence retrieved and all the available studies were conducted or supported by Abbott Laboratories. Most of the papers were conference proceedings and poster presentations on evaluation of CELL-DYN Sapphire™. Only one full article retrieved.

5.1 SAFETY

CD- Sapphire is categorized as a class 2 medical device. CELL-DYN Sapphire™ received 510(k) clearance from the U.S Food and Drug Administration on 25 July 2005.³

There was no further evidence retrieved on safety aspects of CELL-DYN Sapphire™.

5.2 EFFICACY/EFFECTIVENESS

A multi-centre evaluation was undertaken in European countries comparing CELL-DYN Sapphire™ against Abbott Cell-Dyn CD4000, Bayer Advia 120 and Beckman Coulter GenS.

⁴ The evaluation suggested similar performance consistency for WBC counts and differentials, RBC parameter measurement and platelet counts for samples with platelet counts above $40 \times 10^9/L$ of all four evaluated analysers. However, the accuracy for platelet counts with thrombocytopenia was relatively poor with evidence of significant overestimations (Advia) and occasional significant discrepancies (all impedance and optical methods) compared to the CD61 immunoplatelet count. The study also showed that there was poor precision of dye scanner reticulocyte methods (GenS and Advia) compared to fluorescence, particularly for samples with reduced reticulocyte counts.⁴

A study on first past efficiency, comparing CELL-DYN Sapphire™ with Beckman Coulter LH750 showed that the two analyzers have good agreement in most of the parameters where $r > 0.95$ except for basophil ($r=0.163$). CELL-DYN Sapphire™ also showed higher

sensitivity and specificity than Beckman Coulter LH750 when manual differential was used as the reference standard.⁵

CELL-DYN Sapphire™ mean platelet volume (MPV) showed an increasing trend as platelet counts decreased with Idiopathic Thrombocytopenia Purpura (ITP) samples having platelet count of $< 10 \times 10^9/L$ when compared to Bayer Advia 120 analyser. Inaccuracy of platelet at low counts, increased MPV, increased reticulated platelets, low MPC and abnormal CD61 morphological pattern of distribution on cytograms are related to the active phase of ITP, therefore these parameters can be useful to diagnose and monitor platelet destruction and can support clinicians during diagnosis and therapy monitoring.⁶

A study evaluating the implementation of a wide range of monoclonal antibodies with CELL-DYN Sapphire™ showed that the populations discrimination were similar to flow cytometry and the processing procedures were easily assimilated with minimal training.⁷

5.3 COST-EFFECTIVENESS

There was no evidence on the cost-effectiveness of CELL-DYN Sapphire™ retrieved.

6. CONCLUSION

CELL-DYN Sapphire™ is a high-end hematology analyser. It has received 510(k) clearance from FDA which means that it can be marketed in United States. There was fair evidence on accuracy of CELL-DYN Sapphire™. No evidence retrieved on safety and cost-effectiveness of the device.

7. RECOMMENDATION

Based on the findings of this review, CELL-DYN Sapphire™ showed potential in extending hematology laboratory practices. However further research is needed to assess the added value of the device to diagnose and manage certain diseases as well as its cost-effectiveness.

8. REFERENCES

1. Sullivan E. Hematology analyzer: from workhorse to thoroughbred. *Lab Med.* 2006;37(5):273-278.
2. Abbott Diagnostics. CELL-DYN Sapphire. Retrieved on 18/11/2007 from http://www.abbottdiagnostics.com/Products/Instruments_by_Platform/default.cfm?sys_id...
3. Abbott announces US 510(k) clearance of CELL-DYN Sapphire™ Hematology Instrument. Abbott [website] retrieved on 18/11/2007 from http://www.abbott.com/global/url/printerFriendly/en_US/on
4. Mellors I, Hardy J, Aarsand A et al. European Multyi-Centre Evaluation of the Abbott cell-dyn sapphire hematology analyser. Conference Poster, ISLH 2005
5. Wright D, Templeton D. A comparative evaluation of two hematology analyzers for first pass efficiency. Conference Poster. AACC 2007.
6. Diquattro M, Gagliano F, Calabro GM et al. ITP in pediatric age: can laboratory hematology support clinicians to diagnose and monitor platelet destruction? Conference Poster, Germany c2007.
7. Johannessen B, Roemer B, Flatmoen L et al. Implementation of monoclonal antibody fluorescence on the Abbott CELL-DYN Sapphire™ hematology analyser: evaluation of lymphoid, myeloid and platelet markers. *Clin. Lab. Haem.* 2006;28:84-96.