Clinical Diagnostics

Cost Efficacy and Value of Time-tested Systems

Several times in the recent past, heads of central laboratories and those in charge of purchasing and procurement in clinics have been faced with the decision as to whether they should invest in new medical technologies. In most instances the criteria for decision-making are clear, demonstrable, and can be evidenced in terms of economic efficiency as well as the medical value of the technology. However, in some instances technological advances are the only driving force for

Collect blood, using accepted venipuncture technique

those offering new products in this sector. For laboratory executives this means that a clear system-based margin must be drawn between new investments in uncertain products on the one hand, and the stable, safe and continued application of time-tested systems and processes on the other.

For several years now there has been a quest for a time-tested, safe, medically stable, financially established and economical principle in medical diagnostics. Human blood for analysis is centrifuged. By this process blood is fractionated into two phases: the blood clot remains below and the serum is collected above. After centrifugation a blood filter is introduced into the centrifuge glass and the serum is filtered. This standardized procedure is used to filter out any residual clots or other components that may still be present in the fluid above.

The purpose of this filtering procedure is to avoid any risk of falsifying the test result and also prevent sedimentation in the instruments used for analysis.

Gel Versus Blood Filter

This standardized procedure is being applied successfully for several years and is now established as a standard in nearly all laboratories. The system is time-tested and absolutely reliable. The use of blood filters produces reliable test substances for the subsequent measurement. The company that has been manufacturing this product so far recently informed its market partners that the above mentioned blood filter will no longer be produced or distributed. It was also stated that the manufacturing companies, after several years of intensive and laborious research, are now backing a procedure that will gradually replace the previous system and also simplify it. A principle based on a gel procedure was developed and the product manufactured according to this principle. Separation gel tubes are in use for a few years now. They were developed to improve the process of pre-analysis. The production of the blood filters was stopped because the manufacturing company presumed that the increasing use of

follow by centrifugation.

separation gel tubes would replace the blood filters. The manufacturer is actively working on marketing and introducing the new gel-based procedure. However, according to users in central laboratories, the market maturity of this procedure is highly disputed, although the technology of analysis instruments has made significant progress.

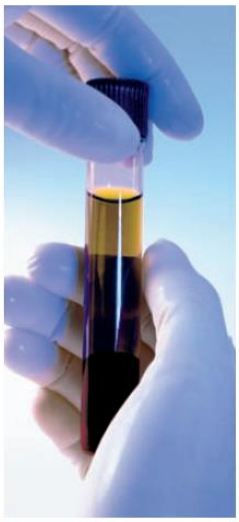
As the production and delivery of the manufacturer's time-tested and esteemed blood filters has been suspended, laboratory executives were now being forced to focus their attention and interest exclusively on the gel-based procedure. In the current environment of cost-sensitivity and economic pressures in the public health sector, requests for investments in new devices and/or systems are received with little enthusiasm by the financial departments of medical clinics.

The situation is rendered more difficult by the fact that personnel – in this case medical laboratory staff – have to be re-trained within the hospital. In addition to new investments, this change involves additional effort in terms of training time and monetary resources for re-training materials.

In every case, decision-makers among the medical staff are mainly concerned with maintenance of the service unit, work processes, and the required purity and reliability of blood samples. One of the aspects of the core competence of a laboratory is its ability to deliver a large number of absolutely reliable blood analysis within a short period of time. This requirement must be fulfilled. It poses a challenge, particularly for medical technology.

Re-launching of Time-tested Products

Based on a market analysis, the managers of Gemü in Switzerland recognized the precarious situation early and developed measures to resolve this critical state of affairs. Within a short period of time, a task force under Lars Rominger was established within the company and empowered with the authorities required to do the job. In a few weeks the task force designed an innovative system-based solu-



Removal of closure.

tion to the problem, based on stringent process-oriented project management. This was the driving force behind the newly developed serum filter Seraclean – a solution to fulfill a specific need, offered at a price in line with market conditions.

The product specifications provide evidence of Gemü's (Switzerland) extensive specialized know-how in the field of system-based solutions in plastics for medicine and the industry.

Market Acceptance from the 0 Series Onward

In numerous conversations and detailed hearings with clinical laboratory executives, both the task force and the executives of Gemü received adequate confirmation of the necessity and appropriateness of this developmental project. A re-launch of a long-standing time-tested serum filter on a high-tech synthetic basis, in line with the highest standards of clean room technology, is a high-level market opportunity. Market partners at all levels of the hierarchy and in all positions have asked for a simple and safe product in alignment with real market conditions. The acceptance of the newly introduced Seraclean filter in the market is an undisputed fact. This was confirmed in several conversations that Lars Rominger held with Dr. Engler and Ms. Bossart from Kantonsspital St. Gallen (Institute for Clinical Chemistry and Hematology), and Lukas Bestmann, Head of the Department of General Analytics from the University Hospital of Zurich (Institute for Clinical Chemistry).

The Direct Advantage for the Client is Self-evident:

The instrument requires no new financial investments in central laboratories. It involves no costly revisions of specialized devices due to gel-induced sediments or obstructions. Seraclean works according to a well established and well known work process.

In order to achieve reliable test results with the GEL procedure as well, Seraclean may be used as an additional process.

Insert Seraclean blood filter into sample tube until the blood cake.

Seraclean has none of the disadvantages of the GEL procedure: disturbances in the instrumental analysis due to infinitesimal quantities of GEL entering the serum; undesired post-coagulation; the gel is not inert and therefore sensitive to cold.

Gels absorb large molecules (e.g. medications) which may falsify the test results.

In contrast to other serum filter procedures Seraclean is very user-friendly and fulfills the highest standards of functionality.

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Seventy staff members are employed by Gemü (private limited company) in Switzerland – a competence center for plastics and medical technology, part of the Gemü group which operates on a worldwide basis, with its head office in the town of Ingelfingen-Criesbach close to Stuttgart (Germany). The Gemü enterprise is active in the fields of medicine, medical technology, the pharmaceutical and food industry, process engineering and microchip production. Processing technology at Gemü in Switzerland focuses on the injection molding of plastics. In this sector the company offers system-based solutions for plastics in the medical industry, in biotechnology, the semiconductor and electronics industry. At the Swiss office in Rotkreuz, extensive resources have been invested over the last few years in clean room concepts for the production of medical-technical products. Gemü engages more than 850 staff members throughout the world.

Serum tube is ready for testing.

The Products and How they Work

Human blood for analysis is centrifuged. By this procedure blood is fractionated into two phases: the blood clot remains below and the serum is collected above. After centrifugation, a blood filter is inserted into the centrifuge glass and the serum filtered by this procedure. The purpose of this standardized process is to filter out any residual clots or other components in the fluid above.

Integrated Additional Technical Value

In contrast to other filter systems Seraclean is equipped with a sealing-lip that never ceases to function because of the specific tool manufacturing technology and the manufacturing processes used to produce this instrument.
Besides, based on a number of detailed technical discussions with laboratory executives and users of serum filters, Seraclean has been designed such that it provides maximum functionality while its application is as user-friendly as possible.

Gel Versus Filter Separation

Expert Opinions

Interview with the specialists Dr. Hanna Engler from Kantonsspital St. Gallen (Institute for Clinical Chemistry and Hematology) and Lukas Bestmann, Head of the Department of General Analytics from the University Hospital of Zurich (Institute for Clinical Chemistry).

Dr. Hanna Engler, Kantonsspital St. Gallen (Institute for Clinical Chemistry and Hematology

Lukas Bestmann, Head of the Department of General Analytics from the University Hospital of Zurich (Institute for Clinical Chemistry)

Hospital Post: **Can you say a few words about your experience with the gel-based procedure?**

H. Engler: Separation gels simplify the work process because they create a division – a layer – between the blood clot and the serum/plasma during the centrifugation step. This layer prevents interaction between the cell components and the blood clot. Besides, the serum/plasma layer can be transferred into a tube (which is then used to transport the sample) by means of simple decantation. This is particularly advantageous for samples which have to be sent to the clinical-chemical laboratory by mail.

The disadvantages of separation gel tubes include the fact that some serum samples may post-coagulate after the centrifugation step, and also gel particles may be released occasionally. If the phenomenon remains undetected it may lead to false test results. In extreme cases these gel particles may cause obstructions in the autoanalyzer system, involving significant costs later on. It should also be remembered that separation gels may not be inert. Thus, the analytes contained in the sample may be re-absorbed. This could lead to falsely low test results and inappropriate clinical decisions.

L. Bestmann: Gels absorb many large molecules such as medications. The values yielded by the analysis may be 40% below the actual value. This does not happen with a filter system. Such false low values can be dangerous. They may distort the general impression – they would falsely indicate that the patient has very low values of a medication in his/her blood; the doctor may increase the dose and the patient may reach a critically high value (in the worst case this could be in the toxic range). Thus, it will be very difficult to steer pharmacological therapy. Besides, gels create technical problems in special devices such as GC-MS, LC-MS, MALDI-TOF etc. Gels may also interfere with certain ELISA's, clog devices, and lead to costly revisions.

What, in your opinion, are the advantages of the serum filter procedure?

H. Engler: Serum filters serve the same purpose as separation gels. They introduce a barrier between the blood clot and the serum/plasma, which prevents pre-analytical problems due to interactions between cell components and serum/plasma. Thus the original tubes can be used in the analytical devices; this permits positive identification of the sample.

As these serum filters are introduced in the sampling tube after the centrifugation step, it is ensured that post-coagulations and other floating particles are removed from the serum/plasma sample. As serum filters can be used with all types of blood sampling tubes, the pipetting step is not required if the blood sampling tube is used without a separating aid.

L. Bestmann: Subsequent orders can be made for a longer period of time because the analyses are falsified more slowly. One example is LDH which, in the absence of a filter, is diffused from red blood cells into plasma after a few hours and generates false high values. When a filter is used, the enzyme is withheld and the clinic may send a subsequent order within 12 hours; this could spare the patient the discomfort of additional blood sampling.

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1-Hour Avian Influenza Test

Global semiconductor maker STMicroelectronics has teamed up with the Singapore medical firm Veredus Laboratories to develop a disposable chip capable of detecting the deadly H5N1 avian flu virus and other forms of influenza within an hour, compared with several hours or days for existing technology.

The diagnostic device is based on STMicroelectronics' In-Check platform, which the company described as a laboratory on a chip, and requires inexpensive peripheral equipment, such as a thermal control system and a reading device, that can be connected to a personal computer. The chip, which is the size of a laboratory glass slide, comprises its own polymerase chain reaction (PCR) which only needs a small sample containing a few DNA strands.

The In-Check technology provides substantial time and cost advantages over existing methods which require much larger samples as well as processing at remote laboratories using expensive, stationary equipment, according to the company.

STMicroelectronics vice-president and general manager for computer peripherals Gian Luca Bertino said the chip is currently in a "pre-industrial phase" and is only expected to be put on the market at the end of the year. He declined to give any details regarding the possible cost of the chip and equipment.

Bertino however added that in the case of an emergency the group could rapidly produce several hundred chips to help health services in the detection of avian flu.

"In the light of the risk of a worldwide flu pandemic, and to limit its potential global impact, we aim to provide healthcare professionals with the capacity to quickly differentiate avian flu or severe flu strains from milder strains by their subtypes", also said Rosemary Tan, chief executive officer of Veredus.

The chip can detect 16 forms of influenza A, as well as three subtypes – H5N1, H5N2 and H5N3 –, and influenza B.

Bertino said that the devices are destined for hospital units but over time their deployment could spread to doctor's surgeries and to retail clients as costs decline.

He noted that the cost of one megabyte of memory fell from 75,000 in 1973 to 0.05 in 2000 to exemplify the rapidity and extent of the price decline in computer processing.

Chip-based testing has "huge potential" and can be used for the detection of infectious diseases, food testing, cancer analysis and genetic disease detection, Bertino said.

The market for chip-based testing is expected to rise an annual average of 31.2% to about US-$ 2 billion in 2008 from slightly more than 1 billion in 2005, according to STMicroelectronics.

The influenza detection chip is the second so-called "lab-on-chip" produced by the semi-conductor giant.

In September, it announced an alliance with the Finnish medical group Mobidiag to produce a lab-on-chip using DNA screening for sepsis.

Bertino said that STMicroelectronics is relying on its partners for regulatory approval and the sale of the equipment.

Nevertheless, the marketing of the products will be studied case-by-case and may be conducted jointly and involve co-branding, the company said.

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Gel Versus Filter Separation

What, in your opinion, are the specific advantages of Seraclean?

H. Engler: Seraclean is introduced in the sample container by means of pressure. The long tube allows the filter to be used for every insertion depth. The material is not brittle. Thus, protruding parts of the filter can be cut away so that the original containers of samples with a very high hematocrit content (large percentage of blood cells and relatively low quantity of serum/plasma) can be used directly in the analyzer even after the filter has been introduced. Another advantage is the rounded upper rim and the hole in the upper end. These reduce the risk of injury and the filter can be pushed directly into the container with the thumb because the air is able to escape during the insertion procedure.

L. Bestmann: Seraclean has no ascending pipe – this makes the filter suitable for the analysis instruments. In devices with an ascending pipe, inexact adjustment may damage pipette needles, and pipette needles are very expensive. As Seraclean is similar to its predecessor, it is easy to handle. Thanks to the long neck of the filter, it can be inserted to the appropriate depth (to the margin of the blood clot) for each sample. The hole at the upper end allows the filter to be pushed downward with the thumb; this causes air to escape during the insertion procedure. Some devices lack this advantage.

What are your expectations of a product that is part of the instrumentation used for clinical diagnostic procedures?

H. Engler: Simplicity, reliability, efficiency, no interaction with analytes or measuring systems, and low extra costs. It would be desirable if the serum filter could be integrated into pre-analytical systems. For instance, automatic insertion and adjustment of the height of the filter in the blood sampling tube. This should occur after the automatized centrifugation step.

L. Bestmann: Reliability, suitability, simplicity, efficiency – preferably, there should be an automatic system of pressing the filter into the blood withdrawal system.

Dr. Engler and Mr. Bestmann – thank you very much for this interesting and informative interview.

Launch of New BNP Test

Axis-Shield plc has completed development of a test for β natriuretic peptide (BNP) that will be distributed by the Diagnostics Division of Abbott Laboratories, for use on its widely-placed IMx benchtop analyser. Axis-Shield produces the test at its Dundee facility. BNP is considered a major marker of chronic congestive heart failure and is a cardiac hormone secreted from heart muscle cells. BNP levels are monitored to diagnose and assess cardiac dysfunction or determine the severity of heart failure. According to the American Heart Association, nearly five million Americans are living with heart failure and 550,000 new cases are diagnosed each year. Axis-Shield already manufactures a very successful test for the same marker, for use on the AxSYM system, Abbott's higher throughput analyser used in hospital laboratories. The availability of the test on the IMx system will facilitate its use in smaller hospital clinics and physicians' offices, particularly in the USA. A very versatile benchtop analyser with a broad assay menu, the IMx system is widely used in hospital and clinical laboratories worldwide.

Investigational Cervical Cancer Vaccine

Merck & Co. announced that the U.S. Food and Drug Administration (FDA) has accepted the Biologics License Application (BLA) for GARDASIL (quadrivalent human papillomavirus types 6, 11, 16, 18, recombinant vaccine) and that the investigational cervical cancer vaccine will be given priority review by the agency. A priority designation is intended for products that address unmet medical needs. Under the Prescription Drug User Fee Act (PDUFA), for BLAs filed in 2005, the FDA's goal is to review and act on BLAs designated as priority review within six months of receipt. The FDA has informed Merck that the review goal date is 8 June 2006.

Since submission to the FDA in December, Merck has also submitted applications for GARDASIL to additional regulatory agencies including those in the European Union and Australia, Mexico, Brazil, Argentina, Taiwan and Singapore.

www.merck.com

High-throughput RNAi Tools

Qiagen and Institut Curie announced a collaboration to develop tools for high-throughput RNAi screening as part of the Institut Curie BioPhenics project. This project, led by Drs. Jacques Camonis and Franck Perez, aims to use RNAi technology in conjunction with advanced systematic phenotypic analysis to accelerate cancer drug discovery. "As one of the largest cancer research centres in Europe, part of the ongoing research at Institut Curie is dedicated to the understanding of how cells become cancerous. The goal of the 'BioPhenics' project is to apply cell biology and microscopic imaging to cancer research for a deeper understanding, improved target validation and, ultimately, more efficient cancer drug discovery", said Jacques Camonis, head of the BioPhenics project in the Translational Department at Institut Curie. "Qiagen is pleased to be able to contribute to this ambitious and exciting research", said Jie Kang, V.P. of R & D. "The combination of Qiagen advanced siRNA design and extremely efficient HiPerFect delivery reagent should contribute greatly to the overall goals of the project."

Inhaled Product For PD

Vectura Group, the drug development company, has received notification from the European Medicines Agency (EMEA) that VR040, its inhaled apomorphine product, has been granted orphan drug designation for the treatment of "off episodes" in patients with Parkinson's disease (PD) who do not respond to oral treatments.