J Lab Med 2008;32(2):59–69 © 2008 by Walter de Gruyter • Berlin • New York. DOI 10.1515/JLM.2008.011

Rationalisation of the pre-analytical and analytical processes of serological infection diagnostics by the use of modular automated systems

Rationalisierung präanalytischer und analytischer Prozesse für die serologische Infektionsdiagnostik mit Hilfe automatischer Systeme

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Abstract

While in large clinical laboratories the implementation of total laboratory automation is continuously proceeding, this concept is mostly not suitable for small- and middle-sized laboratories or for testing laboratories of blood donation services due to costs and required space. For these facilities, however, a rational level of automation can be achieved by the installation of stand-alone work cells for pre-analytical and selected analytical processes. In this review, the features of some automated pre-analytical sample processing systems and automated systems for the serological testing for infectious diseases are described exemplarily and compared with each other. The major advantages of automated systems, compared to a solely manual workflow, are described. Essential factors which have to be considered for making the choice for an appropriate automated system are pointed out.

Keywords: automation; pre-analytical system; serological testing for infectious diseases.

Zusammenfassung

Während in großen klinischen Laboratorien die Einführung der totalen Laborautomation weiter fortschreitet, kann dieses Konzept für kleine und mittelgroße Laboratorien oder Testlaboratorien von Blutspendediensten aufgrund der hohen Kosten und des Platzbedarfs in den meisten Fällen als nicht geeignet angesehen werden. Für solche Einrichtungen kann eine rationelle Automation durch die Installation von einzeln stehenden „automatisierten Zellen“ für präanalytische und ausgewählte analytische Prozesse erzielt werden. In dieser Übersichtsarbeit werden die Charakteristika einiger automatisierter präanalytischer Probenverarbeitungssysteme und automatisierter Systeme für die serologische Infektionsdiagnostik exemplarisch beschrieben und miteinander verglichen. Die wesentlichen Vorteile von automatisierten Systemen im Vergleich zu einem ausschließlich manuellen Arbeitsablauf werden dargestellt. Essentielle Faktoren, die bei der Wahl eines geeigneten automatisierten Systems berücksichtigt werden müssen, werden hervorgehoben.

Schlüsselwörter: Automation; Infektionsserologie; präanalytische Systeme.

Introduction

While in large clinical laboratories the implementation of total laboratory automation is continuously proceeding, this concept is mostly not suitable for small- and middle-sized clinical laboratories or testing laboratories of blood donation services due to costs and required space. The advantages of automated systems nevertheless have to be renounced, as there are several stand-alone systems available which allow the automation of critical work steps. In particular, the pre-analytical processes (e.g., sorting, decapping and aliquoting of samples) are both very labour-intensive and error-prone. Thus, the employment of an automated system for these work steps helps to decrease the workload of the staff and to avoid typical human failures, such as mixing up of samples or pipetting errors. In the following, the features of three automated pre-analytical sample processing systems, the Genesis FE500™ (Tecan Deutschland GmbH, Crailsheim, Germany), the OLA2500 (Olympus Medical Systems Europa GmbH, Hamburg, Germany) and the PVS Sample Distribution System (Sarstedt AG & Co., Nürnbrecht, Germany) are described exemplarily. These front-end systems excel in a high flexibility of the sample output area and can be used in combination with various auto-

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mated analytical systems. Further quality criteria of pre-analytical sample processing systems are the flexibility concerning sample tube types, i.e., the flexibility of the system to process sample tubes from different manufacturers and/or different sample tube sizes. The sample throughput of the system compared to the sample numbers which have to be processed in a given time also has to be considered. Factors which improve the user convenience and which are of importance with regard to the accreditation of laboratories, such as computerised support of quality control and system maintenance, capability of bi-directional data exchange with the laboratory information management system (LIMS), and extent of electronic documentation have to be taken into account.

Regarding automation of analytical processes, the respective testing systems are designed for the needs of the target user group. This holds especially true for the automation of serological testing for infectious diseases. The two major target groups of these systems are clinical laboratories and blood donation services. Therefore, some automated serological testing systems, such as the Abbott PRISM® or the Dade Behring Quadriga BeFree™, are restricted to the use in transfusion medicine due to the limited range of assays which currently can be processed by these systems. Besides the availability of a spectrum of assays which meets the needs of the user as well as the performance of these assays, the above mentioned quality criteria can also be applied to the automated serological testing systems. The common characteristics, as well as the differences, of some established systems are outlined below.

Automated pre-analytical sample processing systems

The Tecan Genesis FE500™

The Genesis FE500™ work cell is capable of pre-sorting tubes, inspecting sample volumes and of centrifugation. Decapping of tubes, aliquoting of samples, destination sorting and sample racking are integrated work steps of the system. The Genesis FE500™ can – under optimal conditions – process up to 500 samples/h. The sample throughput strongly depends on the batch size (preferably batches >200 samples), as well as on the percentage of samples to be centrifuged and the number of aliquots to be generated [1]. Compared to other pre-analytical systems, the Genesis FE500™ is very small-sized ($230\times93\times173$ cm), but nevertheless comprises all typical features of a front-end system.

The tube loading unit of the Genesis FE500™ accommodates up to 80 tubes at one time and provides a continuous loading function. Glass and plastic tubes with a diameter of 11.5 up to 16 mm and a height of 65 up to 100 mm can be processed. In the tube loading unit, a pre-sorting of samples is already performed to streamline the workflow.

The Genesis FE500™ optionally comprises a fully automated centrifuge with a 72 tube capacity. This allows for the integration of a centrifugation step into the pre-analytical workflow. Samples are automatically balanced, as well as loaded and unloaded from the centrifuge, which is placed below the deck. The time needed for loading and unloading the tubes amounts to 5 min for the maximal load. Centrifugation time, speed and temperature are user-definable. This provides a flexible treatment of samples designated for special analyses. Samples not to be centrifuged bypass the centrifugation unit and are directly loaded onto the conveyor system.

The tube inspection unit is equipped with a special laser beam which penetrates up to three overlapping layers of different labels onto the tube for evaluating the tube contents. For optimised performance, the tube can be rotated automatically to obtain access to the best reading window. In the tube inspection unit, the identification of the separation layers (tube bottom, cruor, gel, serum/plasma and air interfaces) takes place. Based on the acquired data, the available sample volume, as well as the remaining volume for archiving, is calculated. The maximum tip immersion depth is assessed to avoid touching of the gel or the cruor during sample aspiration. The measured values are transmitted to the aliquoting unit and to the laboratory software. Suspicious samples are identified and put aside.

The sample transport within the Genesis FE500™ system is realised by a dual-lane conveyor system. This unit provides continuous monitoring of the sample flow through sample barcode and carrier identification.

The decapping unit is able to handle standard as well as screwed caps. For decapping, the tube is moved into an aerosol-protected stainless steel casing to minimise contamination and infection hazards. Up to 400 tubes/h can pass the decapping unit. The Genesis FE500™ provides sample selective decapping based on user definable rules.

The Genesis FE500™ system comprises a secondary tube supply with enough capacity for stocking up to 1500 secondary tubes with a diameter of 13 mm and a height of 75 mm. A thermo-transfer printer with a stock of approximately 8500 labels is integrated into the secondary tube supply unit. Each secondary tube is labelled automatically with a user definable barcode and text label before being transferred to the aliquoting unit. The aliquoting unit requires positive primary and secondary barcode identification. Aliquots of 50–3000 μL can be produced according to the specific needs of the user. The aliquot arm uses disposable tips to avoid contaminations. The disposable tip supply (1000 μL pipette tips) contains up to 288 tips. During the aliquoting process, both (serum/plasma) volume and clot detection is performed.

The completely configurable sample racking unit accepts various analyser racks from different manufacturers. The worktable of this unit can be divided into up to 31 different destination sectors.

The Genesis FE500™ software is capable of a bi-directional exchange with the LIMS, and it provides real-time feedback on all modules. All important information is displayed on one screen. The software also includes a validation programme which ensures that the system performance meets the specifications. The process documentation meets the requirements of the IVD (In-vitro-diagnostics) directive.

The Olympus OLA2500

The OLA2500 is an open sample management system for sorting, decapping, pooling and aliquoting of sample tubes. All tube types with a diameter of 10 up to 17 mm and a height of 70 up to 110 mm can be handled by the system. The OLA2500 is available in four different configurations, as sorter only or as sorting and aliquoting system each in a standard, as well as in a high-speed, version. The standard systems are capable of decapping, sorting and, where appropriate, archiving of up to 800 samples/h. The high-speed version can process up to 1200 sample tubes/h.

The input area of the OLA2500 can be adapted to the individual needs of the user. Up to 300 sample tubes can be loaded at the same time in standard racks or directly in centrifugation buckets. Both primary and secondary, as well as open and closed, tubes can be processed simultaneously. The OLA2500 provides sample selective decapping based on user definable sorting rules. An integrated digital camera photographs each tube for automatic tube type and cap colour recognition, as well as for level detection and subsequent sample volume calculation. For short samples, a priority list for processing can be created by the user.

The samples can be distributed by the OLA2500 to a user definable number of secondary tubes or deep-well microplates without any carryover. The respective microplates are assigned to each sample by positive barcode identification. The aliquoting is performed using special disposable tips which allow for pipetting volumes of 30–920 μL and which can be controlled by positive dispense monitoring. A stock of 420 tips can be stored onboard. Each secondary tube is automatically labelled with a barcode, which contains all necessary information. The system is also able to perform sample pooling for NAT (nucleid acid amplification technology) testing. Positive barcode identification then prevents mixing up of samples. Conductivity measuring during sample take-up, as well as positive dispensing verification by weighing of the pool tube, guarantee an accurate pooling process. Short samples are automatically marked and put aside. Pressure transducers provide automated clot detection.

The OLA2500 is an open system which allows for direct sorting of sample tubes into the analyser racks of all commonly used automated testing systems. The system provides flexibility concerning adaptability to future developments, such as new rack types.

The OLA2500 is capable of a bi-directional exchange of information with the LIMS. Alternatively, Olympus offers a sorting drive software for the OLA2500. The system provides a complete documentation of the sample flow, as well as all microplate and pool population data.

The Sarstedt PVS

The PVS sample management system can be configured individually according to the needs of the user. The standard version includes sorting, decapping and recapping of sample tubes. Optionally, additional modules for sample volume calculation, as well as sample aliquoting, into secondary tubes and deep-well plates can be integrated which, however, leads to a significant decrease of sample throughput (see below).

The input area of the PVS is equipped with a continuous loading function. Various rack formats and centrifugation buckets can be placed onto the tube loading area. All tubes with a diameter of 13 up to 16 mm and a height of 75 up to 100 mm can be handled routinely. For divergent tube sizes, the compatibility has to be checked. The samples can be sorted by barcode recognition, by cap colour identification, or alternatively by tube type recognition. Optionally, a special module for sample volume calculation can be integrated into the system. For correct performance of level detection and sample volume calculation, the tube must provide an unlabelled reading window with a minimum width of 6 mm. Short samples can then be recognised and put aside.

When no aliquoting of samples is performed, the PVS can process up to 1400 samples/h. An optional aliquoting unit with a single aliquoting arm can easily be integrated; aliquoting of samples reduces the throughput to 400 samples/h. Up to 600 disposable tips with a volume of 1000 μL can be stored onboard; the application of smaller disposable tips is also possible. A stock of 250 secondary tubes which are automatically barcode labelled can also be stored in the aliquoting unit. The minimal aliquoting volume is 50 μL; the maximal volume is defined by the total volume of the respective sample. The aliquoting process is monitored by liquid level detection, as well as detection of clots, foam and short samples.

A special feature of the PVS is the capability of recapping of samples. For this purpose, universal lamella plugs are used which can be decapped again by the system if necessary.

The open sample racking unit accepts all commonly used analyser racks and can be easily adapted to new rack formats.

Table 1 Comparison of the features of the described pre-analytical sample processing systems.

	Tecan Genesis FE500™	Olympus OLA 2500	Sarstedt PVS
Applicable tubes	Diameter: 11.5–16 mm Height: 65–100 mm	Diameter: 10–17 mm Height: 70–110 mm	Diameter: 13–16 mm Height: 75–100 mm
Sample throughput	Min.: 100 samples/h Max.: 500 samples/h Mean: 200 samples/h	800/1200 samples/h (standard/high speed version)	1400/ca. 400 samples/h (without/with aliquoting)
Integrated centrifuge	Yes (optionally)	Not available	Not available in standard version, optional integration possible
Sample sorting	Yes	Yes	Yes
Sample volume calculation	Yes	Yes	Yes
Decapping	Yes	Yes	Yes
Pooling	Not available	Yes	Not available
Aliquoting/number of aliquots	Yes (50–3000 μL)/unlimited	Yes (30–920 μL)/6	Yes (50 μL – total sample volume) (optionally)/unlimited
Disposable tip supply	288 tips	420 tips	600 tips (optionally)
Monitoring of correct pipetting	Yes	Yes	Yes (optionally)
Labelling of secondary tubes	Yes	Yes	Yes (optionally)
Recapping	Not available	Not available	Yes
Configurable sample racking unit	Yes	Yes	Yes
Communication with LIMS	Yes	Yes	Yes
Necessity of air conditioning	Recommended by the manufacturer	Recommended by the manufacturer	Recommended by the manufacturer

The PVS continuously exchanges data with the LIMS. The detailed processing protocol data can be transmitted individually for each sample or in datasets for sample batches. Individual stored samples can easily be retrieved for retesting if special barcoded storage racks are used.

A summary and comparison of the features of the described preanalytical automation systems is provided in Table 1.

Automated serological testing systems

Generally, the automated serological testing systems can be classified into two different types: “closed” systems which can only process special assays directly designed by the manufacturer and “open” systems which can process various assays independently of the manufacturer (Table 2).

Table 2 Throughput of the OCD system depending on system configuration and number of different tests.

ML STAR IVD configuration	ML FAME configuration	Throughput per 7-h shift
8 channels	16/20	One test per sample: 1980 samples
12 channels	24/20	One test per sample: 2790 samples
12 channels	16/20	Four tests per sample: 450 samples (1800 tests)
12 channels	24/20	Four tests per sample: 540 samples (2160 tests)

The Abbott systems: AxSYM®, PRISM® and ARCHITECT®

Abbott offers three major systems in Germany: the AxSYM®, the ARCHITECT® and the PRISM® system. The latter has been designed to meet the special needs of a high throughput blood donation service, whereas the others are also suitable for the use in clinical laboratories. The Abbot systems are closed systems, i.e., only defined tests which are designed for the particular system can be processed.

The AxSYM® system

The AxSYM® system was introduced in 1994. It is applicable both in blood banking facilities and in clinical chemistry laboratories. The testing methods applied are microparticle immunoassay and fluorescence polarisation immunoassay. Up to 20 different test parameters can be processed simultaneously by the AxSYM® system, including various serological infection parameters (see Table 3). Currently, there is no syphilis test available which is compatible with the AxSYM® system.

Primary tubes with a diameter of 12 to 16 mm and a height of 93 to 102 mm, as well as secondary tubes with a diameter of 12 to 16 mm and a height of 64 to 76 mm, can be processed. The AxSYM® system can handle tubes with and without a gel layer. Serum as well as plasma samples can be applied. The sample racks cannot be centrifuged, but can be filled by various pre-analytical sorting systems. Samples are distributed by integrated needles with a carryover rate of <0.1 ppm. The precision

Table 3 Comparison of the features of the described automated serological testing systems.

	Abbott PRISM®	Abbot AxSYM®	Abbot ARCHITECT® *i*2000$_{SR}$	BioRad ELITE™	Dade Behring Quadriga BeFree™	Ortho STARFAME Combo
Open/closed system	Closed	Closed	Closed	Open	Open	Open
Available infection tests	• HBsAg • HBsAg confirmation • Anti-HBc • Anti-HCV • HIV Ag/Ab Combo • Anti-HTLV I/II Under development: • HCV Ag/Ab Combo • Chagas • Malaria	• HBsAg • HBsAg confirmation • Anti-HBc total • Anti-HBc IgM • Anti-HCV • HIV Ag/Ab Combo • Syphilis (TPPA) • Anti-CMV IgG • Anti-CMV IgM • Anti-HAV IgGI • Anti-HAV IgM • HBeAg • Anti-HBe • Rubella IgG • Rubella IgM • Toxoplasmosis IgG • Toxoplasmosis IgM Under development: • HCV Ag/Ab Combo • HCV Ag • CMV avidity • Toxoplasmosis avidity • Anti-HTLV I/II	• HBsAg • HBsAg confirmation • Anti-HBc total • Anti-HBc IgM • Anti-HCV • HIV Ag/Ab Combo • Anti-CMV IgG • Anti-CMV IgM • Anti-HAV total • Anti-HAV IgM • HbeAg • Anti-Hbe • Rubella IgG • Rubella IgM Under development: • HCV Ag/Ab Combo • HTLV I/II • HCV Ag • CMV avidity • Toxoplasmosis IgG • Toxoplasmosis IgM • Toxoplasmosis avidity	• HBsAg • Anti-HBc • HCV Ag/Ab Combo • HIV Ag/Ab Combo • Syphilis EIA • Anti-CMV total • HTLV I/II • HCV Ab	• HBsAg • HBsAg confirmation • Anti-HBc • Anti-HCV • Anti-HIV • Syphilis ELISA • Anti-CMV total • Parvovirus B 19 IgG	Any microplate based ELISA can be processed
Other tests which can be processed by the system	Currently none	AxSym Plus: • Various toxicological tests • Fertility tests • Cardiologic parameters • Thyroid markers • Tumour markers • Drug level • Metabolism parameters	• Fertility tests • Cardiologic parameters • Thyroid markers • Tumour markers • Drug level (including immunosuppression drugs) • Metabolism parameters	Adaptability to other Microplate based ELISAs	Adaptability to other microplate based ELISAs	Any microplate based ELISA can be processed
Testing method	Chemiluminescence	• Microparticle immunoassay • Fluorescence polarisation immunoassay	Chemiluminescence	Microplate based ELISA	Microplate based ELISA	Microplate based ELISA

Table 3 (Continued)

	Abbott PRISM®	Abbot AxSYM®	Abbot ARCHITECT® $i2000_{SR}$	BioRad ELITE™	Dade Behring Quadriga BeFree™	Ortho STARFAME Combo
Applicable tubes	No information available	• Primary tubes: Diameter: 12–16 mm Height: 93–102 mm • Secondary tubes: Diameter: 12–16 mm Height: 64–76 mm	Diameter: 10–16 mm Height: 75–100 mm	No information available	Diameter: 11–16 mm	No information available
Centrifugable sample racks	No	No	Yes	No	No	No
Compatibility with front-end systems	Yes	Yes	Yes	Yes	Yes	Yes
Sample distribution	Disposable tips	Needles, carryover rate <1 ppm	Needles, carryover rate <1 ppm	Disposable tips	Teflon®-coated needles	Disposable tips
Monitoring of correct pipetting	• Liquid level detection • Pressure difference measuring	Pressure difference measuring	Pressure difference measuring	• Triple technology for liquid pipetting verification: capacitive, Total Aspiration and Dispense monitoring (TADM) and colorimetric for both sample and reagent	• Liquid level detection • Detection of clots, foam and short samples • Deposition proof monitoring	• Liquid level detection • Detection of clots, foam and short samples by total aspiration and dispense monitoring • Constant pressure monitoring
Sample throughput	160 samples/h corresponding to 800 tests/h	60–120 tests/h	200 tests/h	• 450–820 tests/h • Up to 24 plates in 7 h time shift	• Up to 440 samples in 5 h, if 3 tests per sample are performed • Up to 264 samples in 5 h, if 5 tests per sample are performed	• Up to 2790 tests per 7 h shift in staggered intervals • Exact number of tests depends on processor configuration and on the number of tests per sample
Waste	1 reaction plate per 16 samples	• 1 matrix cell and 1 reaction cartridge/sample • 640 mL liquid waste/h	• 1 reaction cartridge/sample • 5.5 L liquid waste/h	• Microplates • Liquid waste	• Microplates • Liquid waste	• Microplates • Liquid waste
Software	• Bi-directional exchange with LIMS • Local memory: 100 test batches • Data storage: disk, storage on CD/USB under development	• Bi-directional exchange with LIMS • Local memory: 1,500 test results +5.000 control results • Data storage: disk	• Bi-directional exchange with LIMS • Local memory: 35,000 test results +50,000 control results • Data storage: CD	• Communication with LIMS and (pre-) analytical systems • Complete electronic documentation of all processes	• Bi-directional exchange with LIMS • Long-term data storage including consolidation of results for individual donors	• Data exchange with LIMS • Complete electronic documentation of all processes • Software controlled maintenance and verification

Table 3 (Continued)

Abbott PRISM®	Abbot AxSYM®	Abbot ARCHITECT® *i*2000$_{SR}$	BioRad ELITE™	Dade Behring Quadriga BeFree™	Ortho STARFAME Combo
			• Unity Real Rime for Control Quality management (including Levey-Jennings rules)		
• Complete electronic documentation of all process steps • Software controlled request for system maintenance		• Complete electronic documentation of all process steps • Quality control package	• Plate or tube archive management	• Complete electronic documentation of all processes • Customizable application protocols • Operator guidance for system maintenance	

mechanics provide high accuracy of pipetting. The sample distribution process is monitored by pressure difference measuring. The AxSYM® system can be loaded with up to 60 primary tubes and offers a throughput of 60–120 tests/h. The walk-away-system provides the possibility of continuous loading of samples, reagents and consumables. The ready-to-use reagents are stable for 336 h within the system (see Table 3).

The software is capable of a bi-directional exchange with the LIMS. The AxSYM® system provides local memory capacity for up to 1500 test results as well as for 5000 control results. The data can also be saved on disk.

The AxSYM® is a medium-sized testing system which shows successful operation within a temperature range of 17°C to 30°C and a relative humidity of 15% to 85%. The operator convenience, as well as the reliability of the AxSYM® system has been improved in the latest configuration, AxSYM® Plus.

The ARCHITECT® *i*2000$_{SR}$ system

The ARCHITECT® *i*2000$_{SR}$ system is a completely automated system amongst others for serological testing for infectious diseases. The ChemiFlex® testing technology used in the assays is a highly sensitive combination of microparticles as solid phase and chemiluminescence measurements as detection system. The novel technology provides assays with very high sensitivity and specificity. All serological tests necessary for the screening of blood donors can be performed by the ARCHITECT® *i*2000$_{SR}$ system. Further infection tests are currently being developed (see Table 3).

Nearly all sample tube types are compatible with the ARCHITECT® *i*2000$_{SR}$ system, any tubes with a diameter of 10–16 mm and a height of 75–100 mm can be used. As opposed to the AxSYM® system, the sample racks of the ARCHITECT® *i*2000$_{SR}$ system can be directly centrifuged. Samples are distributed by integrated needles with a carryover rate of <0.1 ppm.

One-step assays and two-step assays are processed in the same time (200 tests/h). The first result is already available after 28 min. The system is equipped with a novel, three-dimensional robotic sample handler which increases productivity by allowing permanent access to the samples, as well as random sample loading, and by providing special emergency positions. Emergency samples can be processed by an additional pipetting arm. The system also allows for an automated re-run of samples. The ARCHITECT® *i*2000$_{SR}$ system provides 25 cooled reagent positions for up to 12,500 tests, the colour coded reagents, as well as the calibration, excel in an onboard stability of 30 days. The reagents are labelled with a 2D barcode which provides information concerning assay, lot number, kit size, shelf life and calibration curve. There are two kit sizes available for 100 and 500 tests, respectively. The extensive stock of consumables which can be reloaded at any time permits a walk-away-time of 5 h. The reagent buffer is continuously reloaded

by the system. The in-process monitoring includes not only positive identification of samples and reagents but also pressure monitoring during pipetting of samples (see Table 3).

The user-friendly software provides access control, complete electronic documentation and a special quality control package. Furthermore, the software is capable of a bi-directional exchange with the LIMS. The ARCHITECT® *i*2000$_{SR}$ system provides local memory capacity for up to 35,000 test results, as well as for 50,000 control results. The data can also be saved on CD.

The ARCHITECT® *i*2000$_{SR}$ is a medium-sized testing system which shows successful operation within a temperature range of 15°C to 30°C and a relative humidity of 10% to 85%.

For facilities with a low number of samples to be tested, a smaller-sized version of the ARCHITECT® system, the ARCHITECT® *i*1000$_{SR}$, will soon be available. This new system will provide a throughput of up to 100 tests/h with an identical range of different tests.

The PRISM® system

The PRISM® system provides GMP (Good Manufacturing Practice) compliant complete automation of serological testing for infectious diseases in blood donation facilities. The ChemiFlex® technology already described above is also used in the PRISM® reagents. The PRISM® system is equipped with six independent channels (including one spare channel) for the testing for anti-HCV, HIV Ag/Ab combo, HBsAg and anti-HBc. Moreover, an HBsAg confirmatory assay and testing for anti-HTLV I/II can be performed. Currently, additional tests for Chagas disease and malaria, as well as a HCV Ag/Ab combo assay, are being developed. For the PRISM® system, no assays for the detection of syphilis or CMV (cytomegalovirus) infection are available, neither can other than infection tests be processed by the system.

Samples are distributed using disposable tips to avoid contaminations. Serum, as well as plasma, samples can be applied. The PRISM® system is capable of processing various tube types, including tubes with a gel barrier. The sample racks cannot be centrifuged, but can be filled by various pre-analytical sorting systems. Direct pipetting of samples out of deep-well plates and other microplates is not possible. The PRISM® system provides high sample throughput (160 samples/h corresponding to 800 tests/h). The first result is available after 54 min, continuously followed by another result every 40 s. Up to 280 samples can be loaded simultaneously. Moreover, the walk-away-system offers continuous sample processing, processing of emergency samples in less than 1 h, and software controlled repeated testing. The reagents can be stored in the onboard refrigerator which provides enough capacity for reagents required for 5,000 tests/assay. The functionality is monitored at each processing step; and the performance of reagents and system is controlled throughout the process. The monitoring system includes positive sample identification during the whole process, monitoring of sample and reagent uptake, as well as dispensing, monitoring of the pump function, necessity of valid controls for the release of results, and validation of critical functions.

The software of the PRISM® system provides complete electronic documentation of test, user, date and time, lot number and shelf life, information about controls, calibrators and their status, sample identifications and results, error codes and brief description, as well as the request for system maintenance. Besides bi-directional data exchange with the LIMS, the PRISM® system provides local memory capacity for up to 100 test batches. The data can also be saved on disk; possibilities for data storage on CD or via USB are currently being developed.

The PRISM® is a large-sized, high throughput testing system which shows successful operation within a temperature range of 15°C to 30°C and a relative humidity of 20% to 80%.

The BioRad ELITE™ system

The CE-IVD and GMP compliant, BioRad ELITE™ system was developed on the basis of the Hamilton MICROLAB STARFAME system consisting of the sampler STAR and the processor FAME. Both elements can be used independently and can be combined according to the individual needs (e.g., two samplers and one processor). The ELITE™ system is not yet established in Germany, but there are systems already installed in Finland, Portugal, France and Italy.

Various microplate assays can be processed by the ELITE™ system, including the MonoLisa® HCV Ag-Ab Ultra which is currently the only HCV Combo test available worldwide. This test excels in a very high sensitivity and specificity and yields positive results 4–5 days after positive results in NAT testing. Further assays for infection diagnostics validated for the ELITE™ system are the MonoLisa® HBsAg Ultra assay which provides full mutant detection, the MonoLisa® Anti-HBc Plus assay, the Genscreen Ultra HIV Ag-Ab Combo assay, the Syphilis TA EIA II, as well as different HTLV I/II assays. Moreover, archiving of samples by dispensing into deep well plates can be performed by the system.

The sampler comprises an eight-channel pipettor arm with independently moveable needles. The disposable tips are fixed by a special hooking mechanism essential for the continuous pressure monitoring which allows liquid level detection, as well as detections of clots, foam, and short samples. The correct performance of the individual pipetting steps can be controlled by the deposition proof monitoring system based on the photometric measuring of the colour shift after each pipetting step. Up to three different tests per sample can be performed simultaneously on up to three different microplates. Samples including controls and conjugates are distributed in 14, 18 and 21 min, respectively, when one, two or three different tests are performed. Up to 928 samples on 29

racks each with 32 positions can be processed simultaneously due to the continuous loading system and the autoload tray. Up to 960 disposable tips can be stocked onboard. Depending on the number of different assays, 450–820 tests/h can be performed (see Table 3). Sample tubes, reagents and microplates are identified by an internal mobile barcode reader, whereas the washing solutions have to be scanned manually. The reagent dispensers each comprise a disposable syringe which is stored in the corresponding reagent container. The syringe has a total volume of 20 mL, whereas the reagent container itself contains a total volume of 100 mL. The respective dispense volume of 20–200 μL/well is dispensed in 5 μL aliquots. The dispensing process includes capacitive liquid level detection. In the wash solution stack, eight containers holding 3 L for each washer can be stored. The filling level of the containers is controlled by capacitive liquid level detection. The wash and rinse solution containers can be exchanged during operation.

The ELITE™ system is available in two different configurations: for large facilities with high sample numbers, the system can be equipped with two washer modules each of them consisting of three rows with eight needles, 24 reagent positions and 20 incubation positions; whereas for smaller facilities, the system can be equipped with one washer module, 16 reagent positions and 20 incubation positions. Several reagent positions can be used for stocking the same reagent. The washer module provides capacitive liquid level detection for each needle. The reader-photometer is equipped with eight measuring channels, as well as one additional reference channel, so that eight wells can be measured simultaneously. The reader can be equipped with up to eight optical filters with wavelengths from 405 to 620 nm. The transport of the microplates to the different modules is coupled to the pipettor arm. The ELITE™ system can be combined with the smaller BioRad Evolis™ system both for further tests and as back-up system. Most of Bio-Rad reagents use common generic reagents: same wash solution, same TMB substrate and same stop solution.

The Ortho Clinical Diagnostics STARFAME Combo

Comparable to the BioRad ELITE™ system, Ortho Clinical Diagnostics (OCD) uses the Hamilton MICROLAB STARFAME system as platform for automation of serological testing for infectious diseases (see Table 2). As already described, this system consists of the pipettor Hamilton MICROLAB STAR IVD and the processor Hamilton MICROLAB FAME. The CE-IVD compliant OCD system is designed as an open system, which can process any microplate based ELISA independent of the manufacturer. Samples, reagents and microplates have to be loaded manually. The system can be configured to match the individual needs of the user concerning sample throughput. As a high throughput version, a 12-channel pipettor can be combined with a processor equipped with 24 reagent positions and 20 incubation positions. In this configuration, 2700 tests per 7-h shift can be performed. Alternatively, the OCD system can be fitted out as a medium throughput version with an eight-channel pipettor and a processor equipped with 16 reagent positions and 20 incubation positions.

Up to 576 sample tubes in 18 sample carriers can be loaded simultaneously. The testing of 88 samples for anti-HIV, anti-HCV and HBsAg, including archiving of samples in additional microplates, is completed after 3 h, the testing of 176 samples after less than 4 h, the testing of 264 samples after approximately 4 h, the testing of 352 samples after 5 h, the testing of 440 samples after less than 6 h, and the testing of 528 samples after less than 7 h. Additional testing of the samples for anti-CMV or testing for HBsAg, anti-HIV and syphilis can be performed in a 15-min longer total time.

The OCD system provides various security and safety features, including access control via pass code and positive identification of sample tubes, reagents and microplates. Furthermore, a constant pressure monitoring is performed throughout the process, including liquid level detection, as well as total aspiration and dispense monitoring. The individual points of the pressure tolerance curve can be adapted to the user's given factors. The software assures a high standard of process documentation and traceability of all process steps. The scheduling software manages the work flow during the entire day while still allowing for changes. The system maintenance is also software controlled.

The Dade Behring Quadriga BeFree™

The Quadriga BeFree™ has been designed for the special demands of blood donor screening. The system consists of one liquid handling platform combined with optionally one or two BEP® III analysers. The open system can process any microplate based ELISA. Amongst others, the Quadriga BeFree™ system is compliant with various Dade Behring tests for the serological screening for infectious diseases. For example, the Enzygnost® HIV Integral II test consists of both an antibody sandwich assay for detection of the HIV p24 antigen and an antigen sandwich assay for detection of anti-HIV 1/2/O IgG and IgM. According to the manufacturer, this HIV Combo assay shows high seroconversion sensitivity yielding a positive result with a specificity of 99.89% up to 7 days earlier than other Combo tests. The Enzygnost® HBsAg 5.0 assay excels in the capability of detecting all HBsAg mutants known so far. It also shows high sensitivity, including seroconversion sensitivity, as well as high specificity. Further well established Dade Behring infection diagnostic tests are the Enzygnost® Anti-HBc monoclonal assay, the Enzygnost® Syphilis assay, the Novagnost® Parvovirus B19 IgG assay and the Enzygnost® Anti-CMV/IgG + IgM assay.

Samples and controls are distributed using Teflon®-coated steel needles, which are decontaminated after

each pipetting cycle to minimise contaminations. The samples are distributed by multi-pipetting into the different tests. Shortly after distribution, the samples are released in batches of 88 samples and are available for other tests. Due to the use of steel needles, contaminations cannot completely be excluded. The reagents are distributed using plastic syringes to eliminate dead volume and possible contaminations.

The Quadriga BeFree™ system is capable of processing all standard tubes with a diameter of 11–16 mm, independently of the manufacturer. Special formats, such as false bottom tubes, may also be employed. The sample tubes can be placed into the Quadriga BeFree™ strip-racks by various established pre-analytical systems. Tube types are identified by means of the respective strip rack.

In less than 5 h, the Quadriga BeFree™ system can process 440 samples when three tests are performed or 264 samples when five tests are performed. Up to six different tests per microplate can be interpreted by the system.

Besides a self-test during initialisation, the monitoring system includes an integrated quality control of positive and negative controls and reagents, as well as microplate identification. During the process, the system demands positive barcode identification of samples, reagents and microplates. Liquid level detection is applied at various process steps to detect air bubbles, clots and short samples. The correct sample transfer from the primary tube to the micro-well is verified by photometric reading. The liquid dispensing is controlled by monitoring of the stepper motor. All incubators are monitored regarding accurate temperature. The photometer is calibrated automatically to guarantee optimal light intensity, and each sample result is confirmed by a second reading.

The user-friendly software provides full process control, including donor and sample management, working list distribution, result collection and interpretation, consolidation of sample results for individual donors, long-term data storage, back-up function, as well as complete documentation of test and validation protocols comprising the individual processing steps. The high flexibility in protocol programming enables the user to customise the application protocols. The software also comprises detailed operator guidance for the daily and weekly system maintenance.

Conclusions

Regarding the rational installation of automated systems into the workflow of a laboratory, various factors have to be considered. First of all, reasonable targets for automation, such as labour-intensive, time-consuming and/or error-prone work steps, have to be identified. These are typically the pre-analytical work steps, e.g., decapping, sorting and, if necessary, aliquoting of samples. With regard to serological testing for infectious diseases, the prevention of cross-contamination is a major factor. Thus, the availability of appropriate safety features of the automated pre-analytical and analytical systems has to be evaluated. These safety measures include the use of disposable tips, the prevention of aerosol formation and of carryover, as well as the correct labelling of secondary tubes or deep-well plates and the traceability of the sample. Moreover, standardisation of the pipetting and especially the incubation steps required for serological analyses can be realised by the use of an automated system. As testing laboratories, including those of blood donation services, underlie the restraints of accreditation and GMP/GLP (Good Laboratory Practice), standardisation of processes, minimisation of influencing factors, including human errors, extensive documentation, as well as traceability of samples, and the respective data over an extended period are mandatory. The fulfilment of these requirements is supported by automated pre-analytical, as well as analytical systems.

Concerning the diversity of automated systems for serological testing for infectious diseases, the user has to make a basic decision for an open or a closed system. Both system types have specific advantages and disadvantages. Closed systems are already optimised and validated with regard to particular assays. Therefore, they can be put into operation without further effort on the side of the user. On the other hand, the user does not have the opportunity to apply tests from other manufacturers which might show better sensitivity and/or specificity. Furthermore, closed systems may be limited to a smaller palette of different assays, and they show only limited adaptability to new testing methods. In contrast, open systems provide high flexibility and adaptability. The manufacturers of the established open systems usually offer a panel of different assays for which the compatibility with the automated system has already been validated. To a large extent, the user can decide freely which assay from which manufacturer he wants to apply. In this case, however, assay and system performance have to be validated and documented according to the national legal requirements. For that reason, real openness of such systems is only given if, in parallel, several automated assays for the detection of the same infection parameter are validated and approved by the inspecting authorities. With regard to testing of blood donors for infectious diseases, automation of serological testing has already been successfully established in many blood donation facilities. Due to the great variety of systems, it is possible to meet almost exactly the needs of any user.

The most important factor for the efficiency of automated systems which also includes a positive relation of costs and performance is the expedient integration of one or several automated work cells into the routine workflow of the laboratory. The numbers of samples which have to be tested within a certain time frame, the distribution of sample receipt during the day (e.g. continuous receipt versus peak times), as well as the required test parameters, play a decisive role for making the

choice for an appropriate system. Furthermore, the required space and the availability of air conditioning which is necessary for the correct function of some of the automated systems have to be considered. Logistics of a reasonable sample flow have to be taken into consideration and organised in advance. The available automated testing systems usually are equipped with prepared interfaces suitable for the connection to various laboratory information management systems. Vice versa, the common LIMS are also set for connection to automated systems of different established manufacturers. Although the technical integration of one or several automated systems usually can easily be accomplished, the compatibility of the different computer interfaces has to be ascertained [2].

References

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