IVD TECHNOLOGY
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LABORATORY AUTOMATION

Efficiency through integration in developing IVD platforms

Autonomous submodules integrate preexisting, certified technology and software into new instruments and IVD system analyzers.

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Figure 1. This large-scale hemostasis analyzer is used in high-volume centralized testing laboratories.
Such chronic conditions and common ailments as diabetes, heart disease, and strep throat require frequent monitoring or timely diagnosis. Today, more medical professionals around the world use large-scale IVD systems and small-scale point-of-care (POC) diagnostic platforms and instrumentation to obtain reliable results for common laboratory tests so that patients can receive appropriate treatments.

Large-scale IVD systems are used extensively in hospitals, blood banks, and forensic science, research, and centralized laboratories that may process thousands of samples per day (see Figure 1). Modern medicine and scientific research rely on diagnostic assays to detect diseases. A broad selection of diagnostic assays are available, ranging from mass sample tests that analyze glucose, hemoglobin, and coagulation, to more-customized panels that are designed to detect infectious diseases or identify specific DNA-based conditions. Increasing economic pressures have driven the need for affordable, reliable, high-throughput, automated IVD analyzers that represent the most cost-efficient processes for less-time-critical laboratory tests.

However, for many medical conditions, time is not always an affordable luxury. The critical demand for immediate test results is a primary driver for the development of POC devices, small-scale IVD platforms that offer high sensitivity, accuracy, rapid turnaround, and ease of use (see Figure 2).

Another factor contributing to the popularity of POC platforms is the cost-efficiency of the small-scale device with regard to specialized tests. Rather than sending samples to centralized labs for analysis with high-volume, mass-sample testing devices, medical professionals can use low-throughput POC platforms that provide more-rapid results at a lower cost. Not unexpectedly, POC devices are in high demand by doctors' offices that are located far from central labs. In addition to the convenience factor, certain samples for many IVDs, such as blood gas, cannot be sent out for testing due to their rapid deterioration. Finally, the miniaturization of certain specialized POC devices has enabled patients to perform many common tests by themselves, often with pocket-sized instruments.

Whether POC systems are used by patients at home to maintain proper blood sugar levels or in doctors' offices in remote villages to diagnose a potentially serious disease, they are becoming increasingly important to patient care. Such systems can determine a multitude of variables (e.g., blood glucose, hemoglobin, DNA, blood gases, coagulation factors) from blood, urine, saliva, and other bodily fluids.

Figure 1. This large-scale hemostasis analyzer is used in high-volume centralized testing laboratories.

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An IVD Analyzer's Origins

Developing and manufacturing IVD systems or instruments requires specialized knowledge, a qualified and experienced interdisciplinary team with a variety of scientific and technical expertise, and a fully equipped laboratory and development facility with, in the best-case scenario, integrated manufacturing capabilities.

Due to the highly complex nature of IVD systems, original equipment manufacturers (OEM) can team up with specialized IVD instrumentation development companies to design and develop the next generation of their diagnostic systems. Both parties bring their previous application and technical knowledge to the partnership in order to develop tailor-made instrument solutions. At the beginning of a cooperative relationship, the overall scope of the project, its intended use, and hardware and software requirements are discussed. System requirements specifications are defined, and outsourced service requirements for medical automation and instrumentation are clarified.

Figure 2. This POC instrument was developed for testing food toxins using fl uorescence detection. The instrument was based on a low-cost 68HC12 microprocessor platform.

The specific services expected from an IVD development company often include the following: feasibility studies; comprehensive turnkey instrument or module development; provision of prototype batches for system evaluation or field trials; transfer of developments into manufacturing; system integration of instrument, software, reagents, and disposables; shipping and logistics services; and after-sale services.

System and software design, prototyping, testing, and system validation comprise the development stage (see Figure 3). This phase also includes the manufacturing of the prototype. An IVD development company must document all production materials, tooling, cost estimates of the bill of materials, build timing, and work procedures. A development company must have rigorous experience with implementing FDA's recommended design controls and ISO-compliant processes. FDA registration and certification of the company is also advised. It is important to note that regulations often vary in different countries, which could affect how a system or device will be marketed.

Figure 3. A large-scale diagnostic system utilizing a three-axis motion robot.

System development is followed by design transfer, and the preproduction and production phases (see Figure 4). During this phase, pilot builds, process validation, regulatory submissions, documentation, manufacturing scale-up, and production unit manufacturing occur. For a small IVD instrument with a single function, the process from development through manufacturing could be completed in less than two years. A larger, more complex system often takes three or more years.

Figure 4. A fluidic submodule is shown in its manufacturing stage.

Platform Modules

With regard to final product results, diagnostic OEMs require superior operation, the ultimate in accuracy, unfailing dependability, and stylish design. With regard to the development process, their objectives are simple: short time to market, and competitive development and manufacturing costs. But how can both of these demands be satisfied?

With the IVD development process time measured in years and the average cost in the millions of dollars, instrumentation projects can be accelerated by repurposing fundamental, proven technologies in the shape of existing, validated platform modules. Such platform modules are previously designed and developed components that have been tested, proven, certified, and used in other IVD systems over a period of time.

Some platform modules can be applied to IVD analyzers for the following types of testing: clinical chemistry applying enzymatic and homogeneous immunoassays, and electrolytes; coagulation; immunology using antibodies or antigens bound on solid phases such as tubes or magnetic beads; and molecular diagnostics using chip-based technologies in conjunction with temperature cycling.

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Challenges and Solutions

Some platform modules are commonplace and are often used in either different types of IVD analyzers (e.g., rotor drives, robotic units, temperature controls, etc.) or one type of analyzer (e.g., detection units, user software modules). Thus, a set of platform modules providing standard, off-the-shelf solutions is preferred. However, even within one analyzer, there are different requirements. For example, rotor sizes vary due to different assay packaging dimensions (e.g., different bottles and reagent packs), throughput, or walkaway time requirements. Therefore, using only a single module for different customer projects may not always be an option. A high level of modularization leads to some overengineering, with some features being included to maintain modularity that are not always required. In such cases, unnecessary costs could be incurred.

To overcome such challenges and keep costs to a minimum, an IVD development company should take one step back and develop autonomous submodules that are independent of such varying requirements. Examples of autonomous submodules include the following: linear drives, multiple axis drives, rotor drives, dilutors, needle and liquid level detection, mix and wash stations, agitation units, photometer modules, and microcomputer basic control shells (see Figure 5).

Exploiting autonomous submodules could save diagnostic OEMs up to 25% in both time and development costs. However, more importantly, the savings over the lifetime of an IVD product are immeasurable, due to the fact that the basic foundation of the system is validated and proven to be robust.

IVD Analyzers Types of Instruments and Platform Modules Required			
Clinical Chemistry/ Enzymatic	Coagulation	Immunology	DNA—Analytics
Customer-specific Software	Customer-specific Software	Customer-specific Software	Customer-specific Software
Ion-Selective Electrodes	Clot Detection	Photomultipliers	2-D Imaging
Photometer, Turbidimetric, Nephelometric		Turbidimetric, Luminescence, Fluorescence	
Wash units		Wash units, Solid-Phase Separation	
Needle Modules, Agitation		Needle Modules, One-way Tips, Agitation	
Dilutors			
Temperature and climate control (cooling, heating, cycling)			
Sample and Reagent Rotors			
xy-, xyz-, z, α-Robotics			
Electronics, Microcomputers, and Embedded Control Software			

Figure 5. IVD analyzers designed to perform different functions can share identical autonomous submodules, thus saving development time and making use of previously developed, proven systems. The resulting advantages of platform technology include short time to market, lower development cost, reliability, and no problems in preliminary stages.

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Reusable Software for IVD Instruments

An important part of the autonomous submodules is the electronics hidden within them (see Figure 6). In addition to having a significant effect on the speed to market and development costs, the embedded software is often the source of the highest risk for a new IVD instrument development effort. Moreover, when the support effort over the lifetime of a product is factored in, poorly developed software code can have a major impact.

Figure 6. Assembly, adjustment, and quality control of an optical module.

FDA's "General Principles of Software Validation: Final Guidance for Industry and FDA Staff" stated that "FDA's analysis of 3140 medical device recalls conducted between 1992 and 1998 reveals that 242 of them (7.7%) are attributable to software failures. Of those software-related recalls, 192 (or 79%) were caused by software defects that were introduced when changes were made to the software after its initial production and distribution."

Software development techniques can improve software code quality and reduce the risk of delays. One successful software design process involves a platform configuration approach in which independent modules are developed for reuse in multiple IVD devices. Such modules are microprocessors running on a common bus structure and are used for various functions for which new instrument software can be reconfigured. The software that makes this possible is based on reusable code components, which are written in object-oriented C++ and are designed to integrate into an optimized real-time operating system. Each separate module can be fully tested independently from the complete system by running scripts from a PC application. Such pretested and validated modules contain the various software drivers and controls required to support the module's function. Such reusable software can be extended as the technology's or instrument's requirements change.

POC instruments are typically smaller, less-automated devices and have fewer identifiable modules per se (see Figure 7). However, internal subsystems such as a graphical LCD display/microcontroller, a photocounter module, and all of the drivers and operating systems of a device would exemplify specific functions controlled by such modules.

Figure 7. This point-of-care instrument is a multiple wavelength spectrophotometer with an integrated printer for patient results.

Some common functions include serial communication, displays, memory access, nonvolatile storage, USB control, and smaller POC device drivers such as analog-to-digital convertors, pulse-width modulators, etc. Unique functions might include image analysis, data analysis, complex graphical display screens, main loop program flow, and data storage structures. While an IVD automated instrument might have eight internal modules (e.g., platter drives, pumps, wash station, display heating, cooling, optics), a small POC device might appear to be one integrated design. In either case, designers adopt user interface software to improve or enhance an instrument's graphical style and ease of use.

Shared Codebase

Each IVD instrument project applying autonomous submodules has the advantage of using a given, validated codebase, leaving only the development of new project-specific software. The codebase allows the device drivers, common services, CPU specific code, and operating system to be prequalified, which reduces the project development time and increases the code quality.

The shared, object-oriented C++ codebase supplies the software for the following capabilities and features:

- Full user interface library, supporting LCDs, touch screens, and buttons capabilities.
- Easy replacement of hardware components. Polymorphic access to devices provides easy replacement of hardware components without affecting other parts of the codebase other than the device driver.
- Nonvolatile storage management supporting rotating data logs, cyclic redundancy checked block memory, and random-access nonvolatile random-access memory, all with protection against data loss or corruption from inopportune power loss, as with during a write cycle.
- Task management, communication stacks, state machine support, software version reporting, device drivers, etc.

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In terms of the time and costs saved during the instrument development process, each of these capabilities and features contributes about 25% to the total. However, the real savings comes over time. Poorly developed software code can be full of bugs, hard to support, and easily broken, which increases the cost of the IVD device over time. In addition, the risk of a latent software design flaw going undetected when the device goes into production is higher, thus becoming the biggest cause for recalled products. Subsequent software verification and validation will be more costly.

Certainly, every IVD manufacturer wants to have a set of reusable functions with the idea of reducing later development efforts. However, in reality, often after spending the time required to develop a device, the technology has lunged forward, and what was accomplished is no longer relevant, unless the manufacturer planned for change in advance. But if an IVD manufacturer has the advantage of leveraging a number of instrument projects for many years, it can implement the platform idea across various levels, from the module approach for IVD instruments to common circuit blocks and software at the detail level (see Figure 8).

Figure 8. An inside view of a modular instrument used for monitoring cancer.

At a high level, platform modules can be designed to be flexible and divisible (i.e., the technology can be used in several ways). For example, in IVD instruments, a rotor module is comprised of a mechanical system (e.g., supports, bearings, sensors, rotor platform, etc.) and a control module (e.g., electronics and software). The communications between modules is well defined (e.g., CANbus) so an IVD manufacturer could replace a module with a newer design without redesigning the system if, for example, it wanted to use a newer generation microprocessor. Mechanics could be modified or changed, and the control electronics could be configured to handle such changes. If manufacturers control all of the design data, they can spin off special versions of or modifications for new instruments. The reusable software codebase is one tool that helps to achieve this ability.

For POC instruments, none of the modules developed for IVD instruments would be used directly. However, the underlying technology is the same and can be transferred to the POC design. Again, the common software code makes such leveraging possible by reusing the low-level drivers, thereby becoming an integration effort to add the necessary technology support to a single control board.

Strong POC Growth Projected

While large-scale IVD instruments continue to be in high demand, recent studies show that smaller, more portable POC units are also growing increasingly popular. An article published in IVD Technology summarized this point:[1]

"The potential growth of the point-of-care (POC) diagnostics market during the next five years is discussed in 'Worldwide Market and Emerging Technologies for Point-of-Care Testing,' a report published by InteLab Corp. (Mission Viejo, CA). The study highlighted the individual sectors in the international POC market, such as hospital bedside, home/self-testing, and physician's office lab (POL), and the factors affecting its development.

"The report indicates the overall POC industry will expand by 10.4%, with some individual sectors growing in excess of this forecast. In 2005, the POC market controlled roughly 35% of the total diagnostics product market, and projections indicate that by 2011, it will maintain 41% of the market.

"Customer demands for improved patient outcomes and reduced healthcare costs are crucial factors influencing the POC industry's growth potential. However, the most important issue affecting the POC testing market's progress is the demand for care delivery outside of a hospital setting. Home/self-testing products comprise the majority of the IVD products market, followed by tests performed in physicians' offices or at hospital bedsides. In the home/self-testing sector, which will see a 10.6% increase from 2006 to 2011, roughly 98% of the tests performed were whole blood glucose tests taken by diabetics.

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"Sales of hospital critical care products and POL tests will grow at an 11.7% compound annual rate by 2011. The increase will be the result of immunoassay expansion and the adoption of more molecular diagnostics in the POL sector, which includes labs ranging from small, sole-practitioner-operated units to large operations serving group practices. The POL product increase will net $2.64 billion by 2011, up from $1.66 billion in 2005.

"Hospital emergency departments, operating rooms, and intermediate care wards comprise the hospital bedside testing sector, which forecasts a 6% increase by 2011. The combined market for hospital bedside POC testing products totaled $1.3 billion in 2005, and is forecast to grow to $2.6 billion by 2011."

Conclusion

As the global IVD market continues to expand, the need for reliable instruments, both large-scale and POC, is steadily increasing. At the same time, economic pressures are driving IVD instrument manufacturers to engineer new ways of lowering development costs without sacrificing quality and dependability, or slowing turnaround time. Platform technology addresses all of these concerns. The repurposing of hardware and software saves time and money up front and over time. Autonomous submodules strip platform technology down to its basic underpinnings, allowing dissimilar analyzers to share common building blocks and engineering innovation to begin at the halfway point of the system. An IVD company with a large library of such autonomous submodules has a distinct advantage over competitors with less experience and fewer electronic components from which to draw. OEMs choosing this approach will also have the advantage of cost-efficiency and speed to market. <<

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