



ACHEMA 2003

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The opening ceremony of the 27th AICHEMA was performed in the Congress Center at the Frankfurt Exhibitions Grounds. From Monday, May 19 2003 the gates to the world's biggest chemical engineering Exhibition/Congress and International Meeting on Chemical Engineering Environmental Protection and Biotechnology were opened to the public for 6 days.

The special technical and trend reports of AICHEMA 2003 exhibition were prepared for publication and released by internet as press information by authorities from DECHEMA. Trend reports covering present and future state of Digital Buses for Instrumentation, Separation Technology, and Laboratory Automation in the Pharmaceutical Research are present in this issue.

Digital Buses for Instrumentation

The first reason that most chemical process engineers investigate the use of a bus-structured system to connect all of the instruments and analytical devices used throughout a process plant is to cut wiring costs. The conventional practice of individually wiring every field device back to a central process controller is not efficient. By comparison, the use of a "multi-drop" or "tree-shaped" bus structure – one that emanates from a controller communications card, and connects to a wide range of field devices – makes point-to-point wiring unnecessary. This cuts the installed cost of such devices by 40% or more. Then, new devices can be added by simply attaching them to the bus. AICHEMA 2003 presented and discuss the latest developments in this field for the process industries.

But it's a digital bus's many other advantages that may prove to be the most important in the long run. For example, a fieldbus-based control-system architecture allows for drastic reductions in wiring, input-output (I/O) subsystems and controllers in the field, and it simplifies enterprise, control and remote I/O networking at the host level. The use of a fieldbus-based control architecture greatly simplifies complex, multi-level control and plant networks, and – perhaps most important – it greatly reduces the need for proprietary interfaces to connect incompatible systems and devices from different manufacturers.

A bus-compatible field device needs to be specifically designed for a particular bus, and it must incorporate a microchip-based communications package. As a result, bus-connected field devices generally cost more than conventional analog and discrete analytical and diagnostic devices, monitors and instruments. But their increased functionality and interconnectability often helps to justify this price differential.

Also, while the installed cost of the first bus-connected device is almost always higher than

comparable, traditionally wired point-to-point devices, as the number of devices grows, the incremental costs associated with adding additional bus-connected devices falls.

Even in the most bus-centric control system, a certain number of traditional, hardwired analog and discrete devices are usually still used. Devices that do not have a bus communications capability, and some extremely fast-response equipment, such as gas valves and emergency-safety-shutdown (ESS) systems, are a couple of examples.

In the beginning, the development of digital-fieldbus technology was complicated by a number of initiatives that seemed to evolve in parallel, and all claimed to be "the industry standard". Eventually it became clear that each bus format offered particular strengths and weaknesses, and no single fieldbus protocol could meet all of the requirements. Now that most advanced automation platforms, such as the DeltaV system from Emerson Process Management (St. Louis, Mo.), Experion PKS from Honeywell (Phoenix, Ariz.), Industrial IT Solutions from ABB (Zurich, Switzerland) or SIMATEC from Siemens (Nürnberg, Germany) support several buses running simultaneously in the same controller architecture, competition between the protocols seems to be decreasing.

Following is a brief description of each of the major bus protocols that are available for instrumentation. They are presented in order from simple to complex, and are divided into actuator/sensor, device, fieldbus and control-network categories. Factors to consider when evaluating different buses include such items as cost; impact on existing plant controls; environmental safety; data-transmission distances; response speed; conduit runs and wall seals; and electromagnetic interference (EMI).

Buses for actuators and sensors

AS-i (Actuator/Sensor-interface) is a two-wire, master-slave network in which power and electronic

signals are carried on a single pair of wires. Originally introduced in Europe for factory automation, AS-i has also gained popularity in the U.S. to connect discrete devices to the process control system. For simple on/off service – such as that provided by on/off valves, switches, solenoids, starters and push-buttons, for example – and installations with short distances between the controller and the devices, AS-i offers a rugged, fast, noise-resistant, and low-cost bus that allows several devices to be attached to a single node.

However, the deficiencies of the AS-i bus include relatively small message size and relatively simple diagnostics. And, although the AS-i bus power exceeds intrinsically safe requirements, several manufacturers of discrete valve communication packages must be certified for hazard classified areas.

Device buses

DeviceNet and **Profibus DP**. The next step up the ladder of bus proficiency and costs are open, byte-level serial communications buses. In chemical process operations, the most common ones are DeviceNet and Profibus DP. Both are supported by numerous hardware and instrument vendors, and both support greater levels of process automation, more complex transmitters and valve actuators.

A number of other open device-level buses available, but they are largely used for factory automation. These include **Interbus**, **FIP**, **Seriplex**, **Modbus**, **LonWorks**, and **Sercos**. The Modbus protocol, however, is used by many chemical process operations to provide serial links at the process-control level.

Both DeviceNet and Profibus DP are cyclical, bi-directional networks. Power and electronic signals are carried on separate wire pairs for the DeviceNet bus, and independent power is required for Profibus DP. But unlike the bit-level AS-i bus, these buses transmit larger (small-to-midsized) packets of information for data and basic analog functions. Therefore, they should be wired with special cables that are manufactured specifically for these buses. In addition to sensor/actuator duty, the DeviceNet and Profibus DP buses are widely used for variable-frequency-drive (VFD) control; current and voltage monitoring; barcode reading; device-level diagnostics; local-panel displays; and intelligent motor control centers (MCC), to name a few. Applicable transmitters include those used to monitor pressure, level, flow and temperature data.

In a plant environment, connecting various field devices using a bus can be very helpful by allowing an operator to interface with the process without having to walk to the control room. An intelligent MCC – especially one with VFD starters – that has been factory-wired and connected with a byte-level bus can provide a large amount analog, status, health and diagnostic information on its display.

DeviceNet is the most popular byte-level bus in North America. Because of the high volume of DeviceNet devices that are available, its communications chips are relatively inexpensive. DeviceNet offers both peer-to-peer and master/slave data exchange, and a device may behave as a client, a server, or both. Its communication is good. Rather than the addressing performed by most networks, prioritized messages are broadcast to all nodes and the nodes individually determine whether messages pertain to them, using embedded identifier functionality.

For the highest data-transmission reliability, the bus has several types of error detection and fault confinement – including Cyclic Redundancy Checking (CRC) and automatic retries – to prevent a faulty node from disrupting communication across the network.

DeviceNet supplies power that exceeds the regulatory restrictions for intrinsic safety. And, a relatively large number of DeviceNet products are available for Hazard Classified areas.

Different dominance of bus systems in application in North America and Europe

While DeviceNet currently dominates the market in North America, Profibus DP is the most widely specified, open byte-level bus in Europe. It is one of several offshoots of the basic Profibus protocol; another is Profibus PA, which is discussed later. Profibus DP is a master/slave bus that can support more than one master. The bus also permits the addition and removal of devices and step-by-step commissioning, without disturbing other devices; and expansions have no effect on devices already in operation – assuming that the host supports such functionality.

Profibus DP diagnostics are extensive, with messages assigned by device, module, and channel for quick location of faults. Unusual for a device-level bus, Profibus DP includes optional extended functions that permit acyclic parallel transmission of alarms and read/write functions. This allows statuses to be read and slave parameters to be optimized, without disturbing control. Isolators and I/O multiplexers are available to make Profibus DP intrinsically safe. Further, numerous classified devices are available for areas with a Class 1/Division 2 hazard classification.

Fieldbuses

The most proficient open digital-instrumentation buses are the block-level types that carry large packets of information. Falling into this category are **Foundation Fieldbus** and **Profibus PA**. Fieldbuses are bi-directional and primarily intended to communicate with intelligent field devices. Unlike sensor- and device-level buses, fieldbus segments carry both signals and device power on the same wires. Devices can also be externally powered.

The primary objectives for developing fieldbuses were: (1) to permit control algorithms to be performed in field instruments, as well as in the central controller; (2) to permit remote calibration, commissioning, diagnostics, and maintenance of field devices; and (3) to provide true device interoperability.

Unlike sensor- and device-level buses, fieldbuses are optimized to continuously transmit messages containing multiple, floating-point process variables. These variables are sampled at the same time, and contain signals relating to respective status. And being digital, fieldbuses eliminate drift in conveying analog signals.

The older **Highway Addressable Remote Transducer (HART)** protocol is sometimes thought of as a fieldbus, but in practice, it isn't. Although it can transmit messages just fine, such capability is achieved by superimposing a digital data signal on top of a conventional, 4–20 mA process signal. HART must therefore follow the restrictions of any 4–20 mA, point-to-point wiring scheme, unless the multi-drop capability is used. Not many hosts support the multi-drop capability, as the transferring rate can be too slow for anything other than monitoring applications.

Fieldbuses tend to be slower than sensor- and device-level buses

In general, fieldbuses tend to be slower than sensor- and device-level buses. This is due to the fact that process control in chemical process operations requires more-intense data communications compared to factory automation. This results from the larger amounts of data that needs to be continuously transmitted, the requirement for intrinsic safety, and the fact that power and electronic data are transmitted over the same wire pair. Both Foundation Fieldbus and Profibus PA operate at 31.25 kilobits/second (kbps) and currently, not many of these systems are actually installed or in use in the field.

Fieldbuses were designed from the start to support intrinsically safe (IS) connections, although the number of devices permitted on an IS bus segment must be sharply reduced, compared to a segment serving a non-IS area. Fortunately, manufacturers of power supplies have recognized this and solutions are becoming increasingly available.

Foundation Fieldbus may be the most versatile of the block-level buses, and was developed from the start as a fieldbus. The application layer defines function blocks, which encapsulate basic process-control configurations or functions (such as PID control, analog input, and so on) and the data traditionally found in a distributed-control system (such as PID and ratio control). This user layer also carries device descriptions, capability files and system management, and allows data acquisition and control functions to be performed across the bus between devices of different

manufacturers. Thus it represents a truly interoperable bus architecture.

In addition, Foundation Fieldbus provides so-called peer-to-peer protocol. Devices can communicate with each other without a host, and they can initiate communications without a specific host command. For example, if a Foundation Fieldbus device experiences a problem, it can send an alarm. This peer-to-peer communication also enables Foundation Fieldbus devices with the appropriate functionality to execute control in the field, independent of the host system.

Profibus PA is an intrinsically safe add-on to the Profibus DP bus, and is primarily used in Europe. The upstream Profibus DP portion, and the 2-wire downstream Profibus PA portion, are connected by either an intelligent link or a segment coupler, depending on the Profibus DP speed that is required. The fact that Profibus PA is an add-on to a device-level bus, and does not incorporate a user layer in its communications stack, limits its versatility compared to Foundation Fieldbus.

Like Profibus DP, Profibus PA permits the addition and removal of devices – and step-by-step commissioning – without disturbing other devices.

Profibus PA is a master-slave protocol. A field device is a slave that can only respond to a command from a master. That means if a Profibus PA device experiences a problem, it cannot report the problem unless the host specifically asks.

Control networks

Ethernet as a fieldbus? Interest in using Ethernet to network field-level devices comes from the desire to combine high-performance connectivity with low cost. For discrete manufacturing, this idea has merit. However, for process automation, the issue becomes more complex.

A process-automation fieldbus has requirements that are very different from those of an office-automation network, including:

1. Extreme environmental conditions
2. The need for intrinsic safety
3. Power and signal transmitted over the same wires (for two-wire devices)
4. Compatibility with existing instrument wiring

Commercial, off-the-shelf Ethernet cannot meet these requirements. Industrial Ethernet – with environmentally hardened components, different memory requirements, and greater robustness – comes closer. But, the cost of adding those capabilities reduces the economic advantage of Ethernet. And industrial Ethernet does not provide intrinsic safety, power and signal over the same wires, or compatibility with standard instrument wiring. Ongoing work with industrial Ethernet is aimed at resolving these issues.

However, until these problems are resolved, the best approach is to use each technology where it is most appropriate: Profibus or Foundation Fieldbus for process automation, and Ethernet, with appropriate extensions, as an automation-system backbone and a link to business systems. Chemical-process companies that wait for an Ethernet-based fieldbus will miss the reduced project costs and increased operational benefits that are available today with Foundation Fieldbus or Profibus.

For new plants or plant managers, a combination of the following control system components offers a realistic balance of simplicity and capability:

5. Foundation Fieldbus or Profibus for basic and advanced regulatory control, and for discrete control associated with regulatory control

6. One type of device or sensor bus for motor control and machine control

7. An Ethernet-based, automation-system backbone, such as Foundation Fieldbus High-Speed Ethernet (HSE)

8. A switch or gateway to the Ethernet business network

In addition, existing plants may have to include other networks for legacy equipment. But in general, it is best to avoid buying devices or systems that require different or proprietary buses.

Separation Technology

For the process industries, choosing the right separation process is essential to ensure the desired product quality and the use of environmentally friendly production methods, and last but not least to reduce costs. At ACHEMA 2003 from 19-24 May 2003 in Frankfurt am Main, exhibitors presented a broad spectrum of improved classical processes and also new technologies for just about all sectors of the process industries. Separation processes are also a main focus of the international Congress Programme.

What often stands between products that languish in research laboratories and those that make it to commercial development is the efficiency of the separation processes that are used to remove unwanted substances and guarantee a final product that meets the desired purity requirements. The efficiency, economy and environmental impact of the separation technologies employed – whether they are used to purify pharmaceutical compounds, make biodegradable polymers, extract chemicals from renewable resources or clean up wastewater – can define the success or failure of the new-product development and can directly impact the feasibility and profitability associated with existing chemical process operations.

Most separations carried out during operations in the chemical process industries (CPI) are achieved by classical separation methods, such as distillation,

solvent extraction, precipitation and filtration. Others require novel technologies, such as supercritical fluid extraction, liquid and catalytic membranes, liquid chromatography, and electrophoresis.

Demand for these newer methods is expected to increase as organic and molecular separation methods are optimized and scaled up to produce purified streams of water, chemicals and biological compounds, while reducing or eliminating the generation of byproduct waste streams and other environmental contaminants that are sometimes produced when conventional separation methods are used.

Membranes – essentially thin layers of porous polymer through which fluid can permeate – are expected to play an increasingly large role in the design and configuration of today's complex separation schemes. Membranes are often the separation technology of choice because they can be customized in many ways, and they offer a cost-effective way to achieve the selectivity that is required by the process.

U.S. demand for membrane materials is forecast to grow by 7.4% from the current level to reach \$2.1 billion in 2006, according to market analysts at The Freedonia Group (Cleveland, Ohio; www.freedoniagroup.com). In volume terms, demand for membrane materials is expected to increase to 1.3 billion square feet by 2006. The total demand for membrane systems (including associated pumps, pipes and vessels) is projected to approach \$6 billion in 2006.

Hybrid separation schemes

Novel separation technologies are often used in tandem with one or more of the classical separation methods, often in a single system. Such combinations are called hybrid separation schemes.

Pervaporation/vapour permeation is a state-of-art technology for the separation of water – organic and methanol organic azeotropes. Typical examples of hybrid systems are found in the combination of distillation and pervaporation/vapour permeation. Distillation concentrates the binary or multi-component mixture close the respective azeotropic composition, the vapour from the distillation column is either directly, or after condensation as a liquid, passed over a membrane which is highly permeable to one component (e.g. water, methanol), but nearly impermeable to other components (organics). By the membrane system either the specified final concentration of the organics can be obtained, or the mixture is further separated in a second distillation column. Thus separations can be achieved which otherwise are complex in nature and energy consuming.

Much of the recent research devoted to hybrid separation schemes has focused on meeting the complex separation needs that are associated with the manufacture of products and processes that support the life sciences. For example, organic acids are typically

produced by fermentation of carbohydrate feedstocks. During the fermentation process, selected microorganisms are used to convert the carbohydrate raw materials into the desired organic acids. Because most of these microorganisms cannot work efficiently under acidic conditions, a base is added to the fermentation vessel, to maintain a high pH. The acid is then produced as a salt, which must be converted to an organic acid outside the fermentation vessel.

Traditionally, the organic salt is converted to the respective acid by acidification with a strong mineral acid, such as sulfuric acid. The salt formed as a by-product must be removed, typically via precipitation, crystallization or filtration, and then either disposed of or sold for secondary use in another market application.

However, a newer hybrid separation scheme is now available, and it offers some distinct advantages over the conventional route. Eurodia Industries (Wissous, France) offers an electro dialysis system with a bipolar membranes (this system is referred to as EDBM) to directly acidify organic salts. This scheme eliminates the formation of unwanted salt by-products. Under the driving force of an electric field, the bipolar membrane can efficiently dissociate water into hydrogen (H⁺) and hydroxyl (OH⁻) ions.

The membrane consists of a layer of anion-exchange membrane and a layer of cation-exchange membrane. The two layers are bound together, either chemically or physically. A good bipolar membrane has a very thin interface, but a very good bond between its two layers of ion exchange membrane and a low voltage drop when exposed to an electric field, and it allows for sufficient diffusion of water from outside the membrane to feed the water-splitting reaction.

When a bipolar membrane is introduced in an electro dialysis stack, it is possible to produce an acid and a base from a salt, instead of only concentrating the salt (or desalting a product). In the case of organic salts, this is because H⁺ ions, generated by the water splitting produced by the bipolar membranes, acidify the organic salt solution.

At the same time, salt cations, either potassium, sodium or ammonium, can combine with the hydroxyl ions generated in the bipolar membranes into the base compartment. The base, which can be reused during the fermentation process to control the pH, is recycled for reuse.

Meanwhile, Nizo Food Research (Ede, Netherlands), and the University of Twente (Twente, Netherlands), use membrane filtration and electro dialysis to isolate bioactive ingredients from natural products. The process, called electromembrane filtration, is more selective than membrane filtration alone, and is said to be less expensive than conventional column chromatography.

The setup for electromembrane filtration is similar to that for a conventional plate-in-frame electro dialysis

system, but the system employs an additional porous membrane filter between the ion exchange membranes. The cell operates with current densities of about 100 A/m². The electric field transports the cationic peptides through the membrane to the negative electrode, thus separating them from the similar-sized neutral and anionic peptides.

Separating hydrocarbons

Some of the earliest applications for hybrid separations have been in enhanced oil recovery (EOR), where the carbon dioxide (CO₂) content is high – 70% or more. Such CO₂-rich natural gas streams are good candidates for membrane separation for removal of all or part of the unwanted acid gas, according to UOP LLC (Des Plaines, Ill), which has done extensive work in this field.

Besides acid gas separation, membrane processes for the separation of steam and higher hydrocarbons for the dew-point span setting of natural gas are about to be launched commercially. A further application is setting the methane number of petroleum gas so that this gas can be used as fuel for gas engines. The proportion of higher hydrocarbons in petroleum gas impairs the knock resistance of the fuel, making it imperative to reduce it to a viable level. This is where membrane processes provide an economic alternative to condensation processes. Membranes have been used in industrial applications for organic vapour separation since around 1990. The first plants were used to separate petrol vapour caused by fuel transfer. Currently over 60% of all petrol stations in Germany are equipped with membrane plants for vapour recovery.

Membrane processes for organic vapour separations are being increasingly applied for the treatment of exhaust air and process gas streams in chemistry, pharmaceuticals and petrochemistry. The majority of prevalent solvents can be separated cost-effectively by membrane techniques. Moreover, from both a technical and an economic point of view hybrid procedures, coupling membrane and adsorption techniques, have established themselves as the processes of choice for petrol vapour recovery and clean-up of solvent-polluted waste air streams with minimal residual pollutants. Two examples of monomer recovery in polymer production are the separation of vinyl chloride in PVC production and the recovery of propylene and polyethylene in the production of these two products.

Membranes for gas separation

The use of cryogenic separation systems to produce industrial gases from air and to separate other gas streams has an economic advantage in applications where high purity or high flowrates are required. However, membrane-based separation provides a lower-cost alternative to cryogenic air separation for

many applications, particularly those that can tolerate slightly lower purity levels.

For example, cryogenic separation systems for separating nitrogen from air routinely produce nitrogen at purities to 99.999999% (1 part per billion) and flowrates to 900,000 ft³/hour. By comparison, commercial membrane-separation systems are typically designed to produce nitrogen at flowrates to 50,000 ft³/day, and purity levels to 99.99%. However, because membranes operate at ambient temperatures, they consume much less energy than cryogenic systems. All of the major industrial gas suppliers – Messer Group (Frankfurt), Linde AG (Wiesbaden, Germany), Air Liquide (Paris), BOC Gases (London), Praxair (Danbury, Conn) and Air Products and Chemicals (Allentown, Pa.) have membrane-based systems in various stages of commercialization.

Separation and recovery of hydrogen from purge gas streams in the production of ammonia is a state-of-art process since several years. Increasingly such membranes are used in refineries to recover hydrogen from off-gases and concentrate it to more than 95% purity for reuse.

Membranes become increasingly competitive with cryogenic processes if a high level of portability is required. For example, membrane modules for producing nitrogen and drying compressed air are widely used by small-volume users, who typically require nitrogen or dry air to be produced at the point of use. Suppliers of plant for drying compressed air by cryogenic or adsorption processes often additionally offer membrane driers. Ultratroc in Flensburg deploys membranes and modules jointly developed with GKSS Research Centre in Geesthacht.

Besides nitrogen production from air, membranes are also employed in oxygen enrichment techniques. The latter require membranes that are highly oxygen-permeable. The Chinese have opened up a new market specializing in the enrichment of combustion air from steam boilers and of the oxygen content of room air in vehicles at heights exceeding 2000 m. These systems have been launched by Leader Science & Technology in Dalian (www.gkss.de).

When conventional polymer membranes are used to separate unwanted CO₂ from industrial exhaust streams (to make them suitable for discharge), the gas stream typically has to be cooled to below 150°C. This cooling requirement consumes energy, and increases the cost of separation. However, Los Alamos National Laboratory (LANL; Los Alamos, N.M.) is developing a high-temperature membrane that can be used to separate and capture CO₂ from industrial exhaust streams without the need for cooling.

LANL's new membrane – a thin-film composite that consists of a polymer film, polybenzimidazole (PBI), on a porous metallic support – is said to be resistant to chemicals and can tolerate operating temperatures up

to 370°C. Its most promising application, in terms of capturing [removing?] CO₂, is the separation of CO₂ from synthesis gas. The combination of a polymer with a metallic support allows this new membrane to be more effective at higher pressures than conventional membranes, according to researchers at Los Alamos.

Hot-gas filtration

Filtration involves the separation of particles from a fluid (liquid or gas) by passage through a permeable medium. By tailoring characteristics such as pore size, shape and uniformity, and type and thickness of the filter media, a given filtration system can be designed to retain specific contaminants.

To clean up or recover products from hot gas streams, ceramic- and metal-based filter elements are available to operate at temperatures of 250–1,600°C. These new gas-cleaning systems operate under high pressures and in chemical environments that would destroy fabric bags.

Because these systems operate at elevated temperatures, they avoid or reduce some of the incidentals associated with using fiber bags, such as cooling the hot gas by diluting it with air. The condensation and sublimation that cause fouling are also avoided, and in cases of incineration, there is no dioxin formation.

Higher cleaning intensities with less cleaning pressure than is typical (0.5–1 MPa) for hot gas filter systems that use jet-pulse cleaning is available in the coupled pressure-pulse (CPP) system, developed by Forschungszentrum Karlsruhe (FZK; Karlsruhe, Germany) and USF Schumacher Umwelt- und Trenntechnik GmbH (Crailsheim, Germany). CPP requires a cleaning-gas pressure that is only 0.05–0.1 MPa higher than system operating pressure. The treatment vessel is divided into inlet and clean-gas sides, using a tube sheet to which the filter elements are attached. The CPP system does not suffer from high-pressure losses or large pressure differentials across the filter and it does not cool the gas stream, which could lead to condensation on the clean side of the filter.

Virus removal

Viruses and bacteria pose a constant threat to products and processes. Unwanted microorganisms can be introduced during the production of biological and bio-therapeutic compounds, destroying thousands of dollars worth of recombinant product.

Routine processing and purification methods provide numerous opportunities to clear viruses from biologically produced pharmaceuticals and other products. Many methods that are used primarily for protein purification also do a good job at removing viruses. These include precipitation, ion exchange, gel filtration, hydrophobic interaction, affinity and

mixed-mode-exchange chromatography, and low-pH buffer elution. These separation methods either inactivate the virus particles, or physically separate them from the product based on size, charge, density, binding affinities, and other differences between the virus and the product.

In addition, other physical and chemical methods are under development to render viruses inactive. However, viral-inactivation treatments can cause a number of side effects, such as protein denaturation (i.e. unwanted modification of the protein structure) and subsequent loss of biological activity. Furthermore, many inactivation methods are only partially effective, due to the presence of resistant viruses or resistant fractions within a population of viruses.

Size-exclusion filtration is relatively independent of product or process conditions. As a result, it is considered to be relatively robust because its effectiveness is independent of changing production parameters. And, because it does not compromise the biological integrity of a product, size exclusion is less likely to induce adverse biological and immunological reactions. In addition, filtration based on size exclusion does not require the use of stabilizers or chemical agents (or the subsequent removal of these agents later).

Pall Corp.'s Life Sciences Div. (East Hills, N.Y.) offers several systems for virus filtration. One is its Ultipor VF Grade DV50, a virus-retentive membrane filter designed for efficient removal of viruses by size exclusion from such fluids as biopharmaceuticals, plasma derivatives, diagnostic reagents, tissue culture media and buffers. Made of modified polyvinylidene fluoride, the pleated filter features extremely narrow pore-size distribution and ultra-low protein binding properties.

Another manufacturer is Millipore Corp. (Bedford, Mass) which markets the Viresolve family of virus-removal for monoclonal antibody processing. The line includes Viresolve NFP capsules and cartridges, and Viresolve NFR, an asymmetric, void-free membrane for higher flowrates and fast operation.

Clean water

Often called "the next oil" for its strategic importance, water is expected soon to be as strategic to global interests as petroleum has been since it was first embargoed by the Organization of Petroleum Exporting Countries in the early 1970s. Continued population growth and industrial development, coupled with the increasing scarcity of fresh water, are driving advances in the separation technologies needed to produce potable and industrial water.

A considerable amount of work is devoted to improving membranes and other filtration systems for water desalination. Companies competing in this area include Hydranautics (Oceanside, Calif.); Koch

Membrane Systems (Wilmington, Mass.); Toray Industries (Ohtsu City, Japan); GE Water (Guelph, Ontario, Canada) and Ionics (Watertown, Mass).

Another giant in the field of separation technologies and water purification is Dow Chemical (Midland, Mich.). The company reports that its liquid-separations business had record revenues in 2001 and is expected to surpass that total in 2002.

Laboratory automation in the pharmaceutical research

Laboratory automation has experienced a massive upsurge in recent years. This trend affects all areas of the laboratory. Automated systems have made it possible to perform routine, work-intensive operations quickly and in conformance with stringent quality standards. However, the demand for laboratory automation is greatest in pharmaceutical R&D environment due to an enormous increase in development costs, especially in the drug discovery sector.

The recognition that research especially in the drug discovery sector remains a protracted and often difficult task is nothing new. Chemists and biologists have to test a myriad of compounds in order to detect a clinical candidate. This research-intensive sector is currently entering a new era. The cost of developing new drugs is exploding. There are very high hopes that genome research can help reduce the time and cost factors. The goal is to develop new targets for active ingredients and to make the pre-clinical development process faster and more efficient. Ten to twelve years still elapse between identification of a potential active ingredient and delivery of a finished drug product.

The question the industry faces is how to develop new pharmaceutical active ingredients more quickly. What avenues are available for reducing development times that would be totally unacceptable in other key technologies? There are limitations to the time that can be saved in clinical testing, and from the safety standpoint that approach is undesirable. Instead, the strategy focuses on attacking the problem at the earliest possible stage in the research process. Identifying genes appears to be a very promising approach. Gene research or genomics is regarded today as the key to the search for new drugs. Cutting-edge technology is used to decode and analyze the complete set of genes in an organism. This method can be used to identify the blueprint for proteins. This blueprint is present in every cell in the form of genes. Knowing the blueprint is an important step on the road to developing new active ingredients, because proteins perform vital body functions. If they are not formed properly, they can cause diseases. Pharmaceutical research is interested in finding proteins on which the new active ingredients display their full action.

High throughput synthesis

Conventional, rational synthesis has been unable to keep up with the pace of development of leads for pharmaceutical research. This is due to the high performance capabilities of current assay test systems, which had to check thousands of new compounds for biological effectiveness every day.

Once the target has been identified, the search for the suitable lead structure begins. This is where automation comes in. Today, a mixture containing many compounds created by combinatorial synthesis can be checked very quickly with the aid of automated machines or workstations, making it easy to filter out the active compounds. The total number of compounds or active ingredients created during combinatorial synthesis, which can run into the hundreds of thousands, is called a library. Hits are extracted from this library, which are further developed and used for test purposes. Chemists only need their own workstation for their particular application, where they can produce their library based on the synthesis. This automated equipment performs very specific tasks depending on the application. The devices are arranged in sequence and communicate to optimize the high-throughput synthesis process. Every reaction in an active ingredient process is different.

Arriving at an optimal result requires repeated development and validation, and this is of course both time-consuming and costly. This means that the goal of new active ingredient development must include other factors in addition to quality and effectiveness. It must also provide a further reduction in the time and of course cost required to create a new library. The preferred solution is to try a new approach to the development process. Efforts are now concentrated on creating small libraries with a higher quality content as opposed to high throughput and large quantities. This means that the chances of subsequently achieving a positive test result have to be higher, and the process must be more efficient. To put it another way, more stringent requirements can lead to better-quality chemistry, and ultimately to better performance (e.g. *Mettler Toledo Bohdan*). In the past, attempts were made using solid phase chemistry to create libraries containing 100,000 substances. Today, small libraries contain only 1,000 substances, but they offer higher quality in terms of purity. The next logical step following synthesis is clean-up, and HPLC is the classic solution.

Here again, the industry is taking a giant step forward by exploiting the potential of supercritical fluid chromatography as a high throughput clean-up system (e.g. *Jasco, Mettler Toledo Berger*). Compared to HPLC, SFC has the advantage that it requires only a fraction of the solvents needed for HPLC. There is no evaporation at the end, and the active ingredient is substantially treated, which means more gentle treatment. If the

substance has the appropriate purity level, for example 90 %, then screening and detection are performed as the next step using multi-functional readers. These automatic devices are also integrated into the high-throughput process (e.g. *Bio-Tek*). The results show whether the substance that has been synthesized has any potential, in other words whether it shows any biological activity. If the result is positive, a decision is made on whether to continue working with the substance or return it to the synthesis group, which will make further modifications to the libraries using organic parallel synthesis (e.g. *Chemspeed*) in order to increase biological activity. Screening is performed next, and if the activity of the substance is satisfactory, the last step, target validation, is carried out.

High-throughput screening

The term screening means that all components in a substance library are systematically analyzed for reactivity with a target. All substances are subjected to the same test process, which is called an assay. If the target is a biological receptor, screening is normally performed to identify those substances in the library that will form a bond with the receptor. The substances found in the screening process are potential candidate active ingredients that influence the function of the affected receptor. Automatic pipetting equipment was introduced to reduce the increasing workload involved in routine screening work. A micro titration plate in 96 or 384 well format is the standard tray for assays, for various types of sample preparations, for series analyses and much more. Given the large number of samples that need to be processed, there was also a need for greater automation of pipetting functions.

By combining pipetting tools, all formats between single micro tubes (e.g. *Hirschmann*) and 1536-well plates can now be handled. This facilitates automation of processes that used to run on two or more pipetting robots (*Beckman, Advanced Chemtec*). Assay formulations are decreasing in size as a result of advances in detection, chip technology and the ability to handle very small volumes of liquid. This reduces the consumption of expensive substances and reagents, providing potential for cost savings. A report (Strategic Directions International, Los Angeles) has shown that 70 % of all screening assays, which in the past were performed using the 96 well format, will soon migrate to the 384 well format.

Today (and this is nothing new) the development phase of a new drug lasts ten years on average. During this time, costs for the large quantities of reagents used can easily add up to several hundred million Euro. To reduce the time and costs involved, the goal is to continually reduce the amount of test substances used and to run processes in parallel. The problem is that with sample volumes of less than one microliter, evaporation losses are so high that it is no longer

possible to use open sample vessels. Sealed microchannels offer a possible solution to this problem. DNA mixtures can be separated in microchannels significantly faster than in glass capillaries or agarose gels. For HTS applications in particular, a parallel configuration of microchannels in micro plate standard format can lead to an enormous reduction in cost. DNA and protein analysis can also be performed quickly and efficiently in microchannels (*Greiner Bio-One, Bio-Rad*). It is estimated that 30% of these traditional assays will soon be conducted using microfluid technology.

In the opinion of a leading manufacturer of automation equipment, modular blocks, which can be upgraded and configured as necessary, hold the key to a successful automation strategy. This particular manufacturer is using designs that are based on open-architecture automation platforms (e.g. *Zymark*). This solution offers enormous advantages in terms of compatibility and adaptability. If for example a new generation of pipettors (*such as Tecan*) or detectors appears on the market, the new devices can be quickly integrated into the ongoing process. The use of modular automation is also on the increase. Stand-alone workstations are being developed that can be integrated into a wide range of operating environments, ranging from semi-automatic operation and full-scale HTS (10,000 to 100,000 tests per day) to ultra HTS at more than 100,000 tests per day (e.g. *Zeiss*).

The Goal is full automation

There are two basic approaches to automation, namely full automation of all work steps involved in a process and partial automation of individual process steps. The goal in the past has been to offer a partial automation solution to handle individual steps in a process separately using individual devices such as pipetting robots, plate washers and plate readers. There was no physical or software-based link between the individual pieces of equipment. Partial automation was used because it provided a way of circumventing incompatibility between equipment supplied by different manufacturers and also because it minimized the size of the investment involved. It means, however, that samples must be manually transferred from one device to the next, and the individual devices act as automation islands.

This solution suffers from some a crucial inherent weakness. Manual transfer steps invariably increase the workload on highly-qualified, expensive laboratory personnel. Particularly when faced with increasing sample throughput, workers are often confronted with the problem of managing workflow planning and control of the process, and there is always a danger that process data and the results of experiments can be mixed up or lost. To eliminate this potential source of error, complete electronic process control as defined in CFR 21 Part 11 has been an FDA requirement since

2000. The way to address this issue is to introduce full automation. This is now the standard solution, and it means full automation of an entire process in a closed system, from the test sample to the result.

Complete solutions fulfill very high pipetting precision requirements, and compared to other solutions they guarantee better conditions for sample incubation and temperature regulation of test reagents. One way of accomplishing this is to provide an enclosed, temperature-controller robotic cell featuring safety door access and a thirty-position work deck in micro titration plate format for processing samples. Multi-functional robotic cells are used today in particular for nucleic acid preparation, transformation, reformatting, substance screening and preparing samples for enzymatic reactions. Robotic units for polymerase chain reaction (PCR) can be used for amplification of more than 100,000 samples per day and are normally linked with a multi-function robot that performs sample logistics. There are robots on the market that can perform fully automatic production of agarose gels and subsequent electrophoresis as well as image analysis of more than 2,000 DNA samples per hour. Single nucleotide polymorphisms (SNP) are currently regarded as the key to the development of new medicines. Now for the first time, there is a completely automated solution on the market to address the increasing demand for automated, high-throughput SNP detection offering 100% data integrity for a wide variety of processes. All of this has advantages when your goal is to fully automate biological processes, making it possible to design robust, reliable systems with higher throughput rates without sacrificing precision (e.g. *Proteodyne*).

Genomics, proteomics, arrays

There is a wealth of information available to scientists today, which can help them to simultaneously investigate the effects of diseases, environmental factors, drugs, medicines and other methods of treatment on thousands of genes. The genes provide blueprints for proteins, but very little is known about the exact function of proteins. Researchers are investigating the complex interaction between proteins and the function of the cell. Some manufacturers are placing more emphasis on genomics and functional proteomics in response to research market requirements. Free-flow electrophoresis (FFE) also has an important role to play. Identification of proteins using FFE is necessary when, for example, protein A bonds to protein B, and protein Z is somehow involved. Using automated FFE, it is possible to separate these proteins from each other. The sample can then be fractionated to make up to 50,000 proteins as opposed to 2,000 to 4,000 in the past (*Tecan*).

In genomics, researchers used to place the active ingredient onto a cell culture. They then waited to see

what happened. Today in the genomics phase, researchers investigate what effect this has on the genome or how the expression pattern changes. Then in the next phase, they look at how the protein pattern changes. As a result, automation will move away from traditional screening, turning instead to genomics and proteomics. This means miniaturization down to the microarray, which is mainly the realm of gene expression where spotting, hybridization and detection are performed. The question then always is how proteins can be bonded so that they change in response to therapeutic treatment.

The analysis of microarrays or DNA chips plays a key role in pharmaceutical research and development, which has now grown into a research industry. DNA microarrays are used to identify genes that play a role in disease. In this process, which was derived from semiconductor technology, a specially coated substrate material (*Schott Nexterion*) is printed with gene material, called probe DNA. There are many existing alternative technologies for doing this, such as contact printing, modified ink jet printing and photolithography. These technologies are developed by ACHEMA exhibitors such as IMM Mainz, Research Center Karlsruhe and Institute for Physical Hightechnology Jena.

Because several hundred thousand gene fragments can be arranged on the substrate, high-throughput hybridization experiments can be conducted in parallel. DNA target molecules taken from cell or tissue materials and identified with a fluorescent marking are placed or spotted on the substrate. If the immobilized probe DNA on the substrate matches the target DNA from the sample material, the two single complimentary strands hybridize into a DNA double strand. The fluorescent marking makes it possible to detect the hybridized DNA molecules. Biochips can make this information available in various ways

depending on the type of chip and the particular process involved. The chips are used in gene expression profiling, gene typing, the recognition of polymorphisms or mutation of a gene sequence. Biochips are of course suitable for use in high-throughput screening applications.

According to an analysis conducted by *Frost&Sullivan*, worldwide turnover of biochips will increase from USD \$531 million in 2000 to USD \$3.34 billion in 2004. This is equivalent to an average annual growth rate of 65%. Biochips are used in diagnostics and pharmaceutical genomics.

As the number of therapeutic targets grows, so too does the number of substances that are available from combinatorial libraries. The discovery of leads and lead optimization continues to develop. The number of substances that can be produced by combinatorial chemistry is one of the main driving forces in the HTS industry. Increased throughput has been accompanied by improved detection methods, which have contributed to the huge success of today's HTS drug discovery programs. The end of the 1990s witnessed the discovery of a large number of potential active ingredient candidates, and high expectations were placed on HTS. The number of substances that are waiting to be tested will increase mainly in combinatorial technologies in the next few years.

CRS, which has its headquarters in Toronto, Canada, unveiled its first distributed motion robotic system, which processes one million tests per day. The goal is to reach an average of 7 million tests per week by 2004. The running rate was 2 million tests per week in 2002 (*Frost&Sullivan*). Pharmaceutical and biotechnology companies look with optimism to the future and are investing heavily, particularly in the rapidly expanding field of genomics, proteomics and nanotechnology.