Automation India

Enabling Global Competitiveness

Issue 12 – March 2008 A newsletter of the Automation Industry Association of India

President's Message

Dear friends,

2008 has begun on an exciting note. We signed an agreement with CII to host 'India Automation 2009' — our first, joint International Automation Exhibition & Conference. This event will provide a platform for many industry verticals to witness automation-enabled, global best practices, deployed in manufacturing and infrastructure. And we return to Hyderabad with the Pharmatech 2008 symposium, being supported by PHARMEXCIL.

According to IMS Health, the world's Top 20 pharmaceutical companies are responsible for roughly 65% of the global production of drugs. This clearly demonstrates that the business is highly global, and consequently the key competencies must be represented on a worldwide basis and be able to demonstrate global compliance. This is the only way, with extensive efforts, extended internal communication and networking, to accumulate experiences, partnerships, exchanges and improved awareness. All of which are needed to serve global customers properly.

Products, Services and Solutions must be compliant, according to the rules. But the people involved in the business are of equal importance. All Staff supporting the regulated industries must be trained on the Good Practices, this includes Management, Marketing personnel, Sales, Project Teams, Sales engineers, Service staff, Documentation specialists, etc.

For AIA, organizing the Pharmatech 2008 is just a first step. We are glad that PHARMEXCIL has supported our learning initiative and in doing so strengthened the possibilities of fulfilling on the global vision of our exporting community. We look forward to taking this partnership forward through other joint initiatives that will promote the capability and business success of our respective member organisations.

This issue, dedicated to the PHARMA AND LIFE SCIENCES industry has Mr Vimal Kapur as our Guest Editor. Mr Vimal Kapur, Managing Director, Honeywell Automation India Limited, and a member of the AIA Executive Council, is widely experienced in plant & process automation and recognized for his good understanding of global markets such as the pharmaceutical industry. I trust you will find his selection of topics apt for your needs.

JP SINGH
Hon. President, AIA

PharmaTech HYDERABAD 2008

Automation Strategies for Global Leadership in Pharmaceutical Industry
7th March 2008, Hyderabad
For more information, www.aia-india.org

From the Guest Editor

Dear Readers,

The Indian Pharmaceutical and Biotech Industry is undergoing a wave of unprecedented change. Much of this is due to factors such as introduction of a new product patent regime, the advent of contract manufacturing, the entry of patent free molecules, drying product pipelines and price erosions.

The Indian Pharmaceutical market stands at fourth largest in terms of volume and thirteenth in terms of value. The Indian Biotech industry too has crossed US$ 2 billion and is projected to be US$ 5 billion by year 2010. Indian Life Sciences industry is going through an inflection point. The inflection point relates to an understanding of operations in global environs by Indian companies and at the same time tapping the potential. India has one of the lowest cost of manufacturing and is also a highly attractive destination for R&D especially in clinical trials and other services.

The role of automation technologies is thus crucial in facilitating processes that enable measurement and control, ensure optimum efficiency and increase productivity. Automation is also the key in maintaining consistency & quality and conforming to safety, environmental and a host of other stringent regulatory standards. Automation which was earlier considered only as a tool for compliances is now getting accepted as way of life and is being viewed as "critical infrastructure". Investments in automation include automating the facility by Building management system, access control for security purpose, Process control system, batch records and Manufacturing executing systems, Enterprise Resource Planning, Supply Chain Management and more

In order to highlight the importance of automation and the solutions offered by it, AIA is organizing, Pharmatech - 2008, a 1 day symposium that brings plant owners, equipment suppliers, project integrators, certification agencies and automation experts together to share experiences that have impacted global competitiveness.

This issue of our newsletter examines the latest in automation trends and technologies for the Life Sciences industry. The articles and case studies address the needs of the industry such as - Manufacturing Executions Systems (MES), Process Controls, Process Analytical Technology (PAT), Track & Trace, Building Control, and more..

Due to globalization and increased competition, automation has become a key differentiator in maintaining a competitive edge. At AIA, we are committed towards understanding & meeting the challenges faced by the Life Sciences industry. Together, along with manufacturers, we hope to mutually understand & facilitate manufacturing processes that bring products to market faster, cheaper and profitably.

VIMAL KAPUR
Member, Executive Council, AIA
& Guest Editor, Automation India

A look at thirty years of change in pharmaceutical automation

The business environment of the pharmaceutical industry is becoming increasingly demanding, where only those companies committed to excellence will thrive. The integration of the control and enterprise systems will allow companies to see and analyze much more information from the manufacturing operations and will allow them to optimize manufacturing.

Growth of Automation

While automation started and progressed slowly in Pharmaceutical Industry, it has come to play an increasingly important role in keeping the industry moving ahead. Pharma lagged while other industries, such as general chemical and specialty chemical, were regularly moving to new technology applications and improving manufacturing performance. But in the past few years, the pace of innovation has accelerated greatly and shows no sign of slowing down. Predictive Intelligence and the field device alerts are gaining importance, aiming at increased availability. Asset Management has become an important part of Automation and is leveraging the best the technology can offer. This article looks at major automation trends in the field from 1977 to the present and gives some ideas on possible future trends.

The old days (pre-1977)

The first programmable logic controller (PLC) debuted in 1969, but its wide-spread use in the pharmaceutical industry was still years, if not decades, away. Channel-based analog equipment was the standard. Single controls — either pneumatic or electronic — were mounted on walls in big racks. There was little if any recording of data other than manual data record keeping by operators, and that was done on paper. Circular chart recorders and strip chart recorders were the main way of recording process parameters.

The late 70s and early 80s

The first distributed control systems (DCSs) came out in 1975. At first used mostly in the chemical industry, DCS began to gain popularity in the Pharmaceutical industries by the latter part of the decade and in the early 80s. The Food and Drug Administration (FDA) was ramping up its regulatory requirements and automation was seen as a good tool to facilitate compliance. Use of this tool accelerated as batch control automation and batch unit operations control became available in 1983. The ability to use “configurable off the shelf” software to write sequences, take automatic actions based on failure, create recipes, and synchronize parallel unit operations delivered significant improvements to manufacturing. Implementing commercial off the shelf (COTS) was a large, challenging task as control rooms and wiring were centralized with everything coming back to a combination of a main control room and a massive main wiring hub. Thinking about batch software logic and failure handling was new to many people.

The late 80s to early 90s

Once people gained experience automating batches, batch standards began to be developed. The goal was to have everyone talking the same language, using well defined terms and having a common architecture. The first batch automation standard, S88 (on which work began in 1988), was approved by ISA in 1995. This standard was initially implemented in two applications: PID's Open Batch and Consilium's Director. These applications became the basis for many of the batch automation solutions that developed around the S88 standard. In addition to developing standards, the World Batch Forum was started in 1994. This forum for the batch process industries focused on best practices in automating and applying technology to batch manufacturing.

By the mid 90s a number of product platforms built on these new standards began to appear. The concept of class-based configuration software was introduced. Class-based software facilitated common libraries of building-block modules linked to unique instances of the modules as they are applied. The library modules are then quickly replicated but change control can also easily be applied as the various instances can maintain the characteristics of the class, making it easy to change them and document the change. While not initially applied to their full extent, these concepts became an enabler for the modular construction approach utilized by most Pharmaceutical companies in the early 00s.

In addition to automation standards, regulatory concerns for managing all the systems automating production and the data being created were being developed. In response to the uncertainty of validating computer systems, end users, automation vendors, and consultants came together to define and standardize practices. In 1994, the Parenteral Drug Association (PDA) issued Technical Report No. 18: Validation of Computer-Related Systems. In 1995 the Good Automated Manufacturing Practice (GAMP) Forum issued the GAMP Guide for Validation of Automated Systems. GAMP became the user community's voice for comments and response to the various governmental regulations. Also, PDA issued Technical Report No. 32 to define good practices for auditing suppliers. Although 21 CFR Part 11 was not

formally issued until 1997, work started on it in the early 90s. Part 11 focused on how to design, implement, test, and manage change with automation systems and the electronic data created. By the late 90s, the focus had clearly begun to shift from applying technology to managing records and proving regulatory compliance.

The late 90s to early 00s

The standardization movement gained momentum as the new century approached and began. Users in the Pharmaceutical industry began to ask for standardized, configurable, off-the-shelf equipment.

Through the second half of the 90s some disruptive technology began to appear, with an aggressive move away from customized hardware development to standard common off the shelf products using Ethernet communications.

Pharmaceutical companies started using distributed hardware and putting Ethernet-enabled I/O in the field. This was followed by the movement of controllers and their cabinets into the field and the centralized control rooms began to be superseded. Yet pharmaceutical companies were quite conservative when it came to adopting the digital field buses that were becoming common in other industries and are only now moving in this direction.

The regulatory burden peaked at the turn of the century with both industry specific regulations like Part 11 and the Y2K computer system concerns. With the enforcement of Part 11, the industry invested in more current technology that better addressed electronic data and records. Many companies scrambled (some without complete success) to achieve compliance. On the one hand, Part 11 helped drive modernization of automation systems, but on the other hand, it contributed to a sense of confusion and panic. Yet because Part 11 spurred the industry to improve user security, data security, and record security, Pharmaceutical companies are generally ahead of chemical and other industries in these areas as well as lot tracking and batch management. For many companies, Y2K and Part 11 were the drivers for modernizing their automation systems.

Then, the regulatory burden began to lighten. In response to the industry, the FDA in 2004 announced their initiative “cGMPs for the 21st Century”. They began to encourage Pharmaceutical companies to apply risk-based approaches and to use more current technology without the fear of validation backlash. As a result we are already seeing among other things, more wide-spread adoption of digital buses and more use of advanced control technologies. Emphasis on systems with built in compliance to S88 and CFR Part 11 is increasing.

Other recent changes

In the last four or five years, there has been an acceleration in the aggressive use of skid-mounted equipment. Companies are trying to buy skids that do water deionization, for example, with all equipment in place and ready to be bolted together. Close on the heels of

this has been the adoption of a modular construction format for plants. While this helped to make the overall build process faster, in combination with the spread of standards and class-based approaches, it also had a significant impact on automation and technology.

Another major change in the last three or four years is the integration of companies from top to bottom. Increasingly, the control system and the enterprise system are connected, although it is important to establish appropriate safeguards to keep intruders from gaining access to vital production data or, worse, hacking into and sabotaging production. Much of this integration is being driven by the conversion from paper to paperless, and will drive the next transformation in how Pharmaceutical companies operate. This integration of the control and enterprise systems will allow companies to see and analyze much more information from the manufacturing operations and will allow them to optimize manufacturing.

Latest automation systems have in-built compliance for S88 and CFR Part 11 to address the industry standards. The current advancements include increasing the ease of integration and leveraging the predictive intelligence of the field devices to increase the availability.

Recently, more companies are taking advantage of Operational Excellence programs. In 1977 or the early 80s, a pharmaceutical company was a research and development, marketing and sales organization with a little black box called manufacturing in the middle. Margins were high and as long as the products went out the door in good order there was little need to look at manufacturing efficiency. This, in fact, was one of the major reasons that pharmaceutical manufacturing has been more conservative than other industries. That has clearly changed. The business is more competitive, customers are increasingly price conscious and manufacturing and supply chain efficiency is increasingly urgent. The plant floor and production are now tied to how the labs work, to timely releases of new products, and to overall profitability. Putting the right kind of automation platform in place can facilitate making this happen.

Another recent trend is flexibility. The industry is moving from products that historically have been produced through organic-based synthesis to biologic products. Biologics are inherently more complex. They may also be targeted to specific groups, even to individuals. The breadth of products requires a great increase in flexibility on the part of the manufacturer.

The business environment of the pharmaceutical industry is becoming increasingly demanding, where only those companies committed to excellence will thrive; those that don't may well find their survival in danger. The challenges are clear to all: decreasing levels of reimbursement, lawsuits, fewer blockbuster discoveries, unexpected competitors, and the list goes on. The solution for most companies today can be summed up as the pursuit of excellence — superiority in operations and execution of business processes — and has come to be called Operational Excellence.

Eye on the Prize

Simply making improvements in a few areas is not enough to achieve Operational Excellence. It requires a level of corporate performance that will garner praise from the investment analysts who advise the actual owners of the company. It requires using the right tools, methods, and advice and combining them with dedication to achieving true world-class status.

It requires constant work, attention to detail, and the honesty to examine one's own shortcomings and correct them, and to never settle for what once worked, or works in some places, but constantly striving for the elusive goal of being the best of the best. Many factors contribute to world-class performance, but the best opportunity for achieving operational excellence is where the money is spent and made: production.

Sathi Kannan, Bob Lenich and Christie Deitz

Critical Instruments and Services using a compliant process based approach

Abstract

The automation industry has served customers in the 'regulated industries' which include Food and Beverages, Fine Chemicals, Pharmaceuticals, Biotechnology, Life Sciences, Cosmetics, delivering process measuring instruments, services and solutions dedicated to the processes of these regulated industries: flow, level, pressure, temperature, analysis, (conductivity, pH, OD, …) and recorders.

From this encompassing product range, tailored solutions combined together with services can be delivered as process automation packages, to be used in existing plants and for new projects. Process solutions are implemented together with end users and third parties, for whom good practices are of vital importance, ensuring the best possible quality for the production of the drugs.

Focus on all the regulated industries and key regulatory requirements

Regulated industries have overlapping areas and are driven by many of the same laws, rules and recommendations. The FDA's regulations will become more and more stringent in the future, and the rules and laws have to be well understood and implemented by the end users as well as by the suppliers.

For this reason the automation suppliers have implemented a compliant strategy, to ensure that products and solutions provide the best possible contribution to the final quality of the manufactured drugs. Achieving this objective means having the ability to deliver compliant packages, instrumentation and measuring solutions, including the associated services. The roadmap of Validation is described in a Corporate Validation Master Plan, justifying the strategy and outlining many relevant aspects including documentation, planning, GxP's areas, GxP's relevant systems, internal rules, trainings, planned activities.

A common understanding for all the partners: GxP's, GAMP4, part 11

The Validation roadmap must ensure policies and procedures comply with the Good Practices developed by the industry. Regarding measurement instruments, the key regulatory requirements are typically those described in the GAMP Good Practice Guide - Calibration Management published by the ISPE 1 January 2002.

Additionally the GAMP4 2 guidance allows companies to achieve validated and compliant automated solutions meeting all current healthcare regulatory expectations, by building upon existing industry good practice in an efficient and effective way. It allows all parties involved to speak the same language and to have a common understanding.

In August 1997, the title 21 of the Code of Federal Regulation Part 11 became effective. It concerns electronic records and signatures. This law is intended to facilitate the use of paperless record keeping systems and provides criteria under which the FDA will consider electronic records to be equivalent to paper records and electronic signatures to be equivalent to handwritten signatures.

The final rule as stated in section 11.1(a) provides “criteria under which the agency considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable and generally equivalent to paper records and handwritten signatures executed on paper”.

This law is executed in two parts: electronic records as described in the subpart B of the part 11 and the electronic signatures described in the subpart C of the part 11.

A specific interpretation of 21 CFR Part 11 should always be considered within the Validation Master Plan in line with the scope of supply.

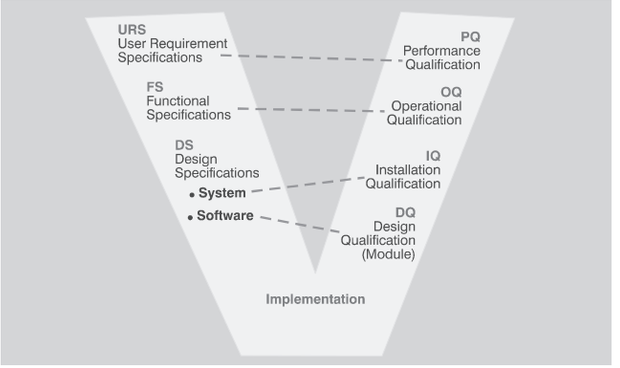
More awareness....less mistakes

The objective is to produce drugs of the highest quality. A critical instrument produced on a compliant process-based approach is a must for all the regulated industries to achieve this target. More awareness on this issue avoids mistakes and provides many benefits:

- Compliance for the end user
- Knowledge benefits:
  - better understanding of the process
  - improved operational efficiency
  - reduced risks of failure
  - maintenance of quality standards
- Business benefits of the Good Practices:
  - reduced operating costs
  - improved profitability

Global compliance for Global business and Global Customers

According to IMS Health, the world’s Top 20 pharmaceutical companies are responsible for roughly 65% of the global production of drugs. This clearly demonstrates that the business is highly global, and consequently the key suppliers must be represented on a worldwide basis and be able to demonstrate global compliance. This is the only way, with extensive efforts, extended internal communication and networking, to accumulate experiences, partnerships, exchanges and improved awareness. All of which are needed to serve global customers properly.



The ‘V-model’ as standard for the regulated industries

Compliant hardware and software, but also skilled people and qualified services

Products, Services and Solutions must be compliant, according to the rules. But the people involved in the business are of equal importance. All Staff supporting the regulated industries must be trained on the Good Practices, this includes Management, Marketing personnel, Sales, Project Teams, Sales engineers, Service staff, Documentation specialists, etc. . . Projects should be quoted according to the Good Practices guidelines by the Sales organisations whilst the products must be assembled and tested accordingly to the relevant SOP's in the Production Centers.

Specific training sessions regarding GxP and in particular 21 CFR part 11 compliance are organised in both production and sales centers and for our IT specialists. Each GxP relevant area has its own action plan and company specific VMPs are implemented where appropriate within the individual countries. Regular on site regular verification and calibration are conducted by qualified service staff trained on Good Practice.

From R&D to . . . decommissioning

Deliverables should be approved in a logical order. A complete life cycle covers the phases of planning, specification, design, construction, testing, installation, acceptance and operation right through to decomissionning of the plant.

The User Requirement Specifications (URS), the Functional Specifications (FS) along with all the different 'V-model' steps are established qualification milestones providing standardization throughout the regulated industries.

The great benefit of this standardization is that it provides a common language, terminology and a comprehensive flow of procedures and tasks which are essential for the implementation of projects and subsequent maintenance.

At the end of its operational life, any system or device should be decommissioned, which may include archiving data. Regulatory or other requirements for the preservation of electronic records should be carefully considered. An archive report should be generated describing the archive approach and listing documents, raw data and electronic records archived. It should be able to retrieve the data even if the original hardware is not anymore available. This data should be retained as required by relevant regulation and user company policy.

Implementation of the latest technologies

The latest Fieldbus digital transmission technologies (Profibus for example) improve substantially the integrity of measurement, increase instrument performance and at the same time help to simplify the documentation. Consequently operating costs can be reduced. It is possible to provide compliant Engineering tasks and documents regarding Fieldbus technologies as well as solutions and tools for qualification and monitoring of sensors and systems using digital technologies.

Many vendors are actively engaged in the PNO group, pushing and developing guidelines and references in order to get the best possible procedures and qualification tools for digital technologies.

Documentation . . . and documentation Management

Ask the following question to a drugs manufacturer "What's your first concern?" He will probably answer "To get a compliant production tool . . . This is my first target!" And even when a production unit is compliant, everything must be documented. This is also the same situation with any product, solution or service: "if it is not documented, it is not done". Documentation is a major part of global compliance.

The purpose of Good Documentation Practice is to ensure that key documents are created, reviewed, approved, distributed and stored in a controlled manner. This should ensure that key documents, such as requirement documents, design documents, as-built documents, tests results, calibration records, etc . . . are used properly and established in a traceable and manageable basis for qualification and validation activities. As a compliant supplier we recognise and support this need from the project design stage right through to provision of tools for calibration management.

Observations and conclusions

It is imperative to understand the manufacturers business, to conceive, design, produce, test and deliver measurement devices, services and solutions with the appropriate features to adequately meet pharmaceutical and regulated industry expectations.

To be able to rely on a partner having accumulated experience, flexibility, understanding, know how and partnership mentality is of premium importance.

Global approach, costs benefits, mutual comprehension, product quality, increased safety and compliance, trained people are the key areas where added value is created, time is saved, and knowledge is developed for all the parties.

The only way to achieve this goal is to implement a compliant processed approach, based on the Good Practices guidelines. This is something like a 'universal and profitable language'.

Acronyms

FDA: Food & Drug Administration

ISPE: International Society for Pharmacoepidemiology

GxP's: Good manufacturing Practises

GAMP: Good Automated Manufacturing Practise

PNO: Profibus Nutzeorganisation (usergroup)

SOP: Standard Operating Procedures

1 ISPE, GAMP Good Manufacturing Practise Guide : Calibration management

2 ISPE, GAMP4 Good Automated Manufacturing Practise

3 2 1 CFR Part 11 - Electronic Records and Signatures Section 11-10(e). Department of Food and Drug Administration.

François Prautois

TRACKING & TRACING

Safe Pack

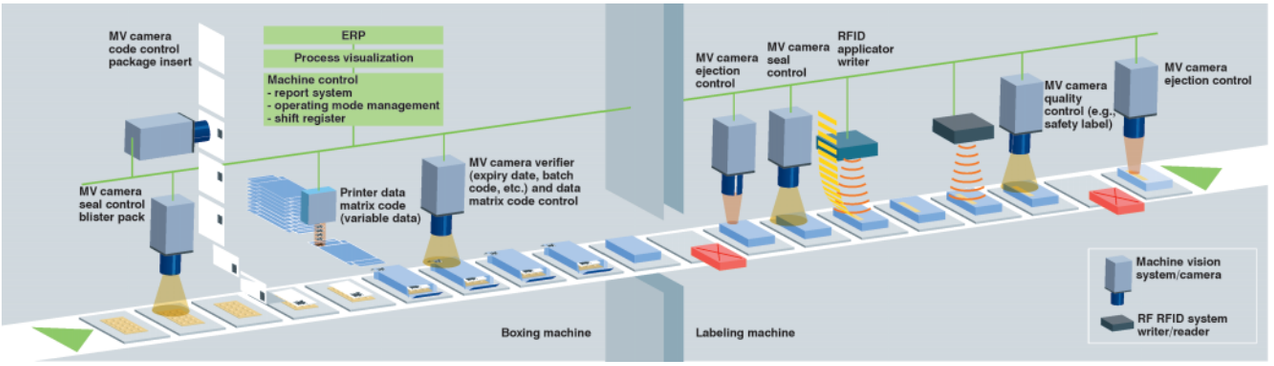
Sensors integrated into the automation system support process-safe packaging that can be easily validated

Authorities are placing increasingly strict demands on the safety of pharmaceutical products. This also includes full manufacturing documentation in which all packaging elements are identified automatically and the packaging process is documented in detail. The strict regulations also necessitate the integration of packaging machines into "track & trace" systems. The correctness of the packaging and package inserts must be documented, while at the same time the correctness and legibility of the product codes printed on the packaging must be ensured because they identify the individual products and therefore serve as a key component of the required proof of quality.

Integrating the functions necessary to meet these specifications into the packaging automation system has many advantages. A packaging solution using this system can be validated easily and quickly. Integration also offers the advantages of fast engineering, rapid commissioning, good serviceability, and efficient diagnosis. The quality status and position of every product on the packaging line can be traced at any time, and master track & trace systems on the IT level are supplied directly with quality data.

Auto ID minimizes risks

Using auto ID in pharmaceutical packaging lines provides positive confirmation that the right packaging materials, package inserts, and leaflets have been used. At the same time, auto ID provides the relation between the individual

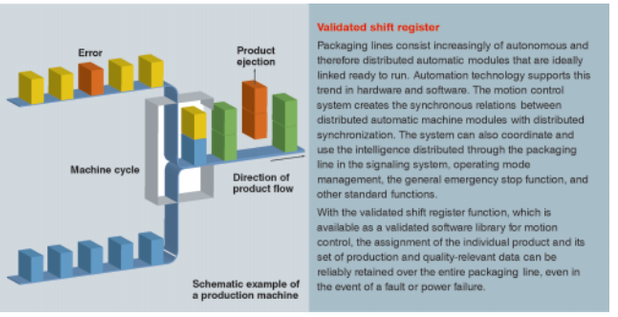


Requirements for the packaging lines

— Reliable automatic identification of all materials used (auto ID)

— Protection of every quality-relevant process step by downstream inspections (e.g., optical seal and label control with machine vision)

— Data flow clocked through every station, which assigns the quality characteristics recorded in the process to every product in a fail-safe procedure (“validated shift register”)



The continuous tracing of the manufacturing process requires automatic identification of all packaging components and ensuring a correct process execution by using machine vision components

product and the corresponding quality data set recorded in the process. This is a prerequisite for the reliable ejection of defective products and is also provable. In a packaging line protected against manual intervention, auto ID prevents defective products from getting into the transport packaging and therefore onto the market. Every detail of the quality of the delivered products can be positively confirmed.

Data matrix or RFID?

Packaging components, package inserts, and leaflets are usually detected automatically by means of bar codes or data matrix codes, but the direct interpretation of text and graphics in printed material is also possible with machine vision technologies. The labeling of pharmaceutical products with an electronic pedigree is already being discussed in some US states.

Data matrix codes are applied to solid and flexible materials at an extremely low cost by various printing methods. The data matrix code can be fully reconstructed even when up to 25 percent of the code area is illegible. Data matrix codes are therefore increasingly preferred to other methods for the labeling of materials and packaging components. However, whether the product code is printed directly on the packaging by using a data matrix code or stored on an radio-frequency identification (RFID) tag on the packaging depends, above all, on the requirements of the target market. So it may be necessary to equip packaging lines with both data matrix and RFID technologies. This also makes the production more flexible. With RFID, in-house logistical processes and distribution benefit from the rapid bulk acquisition of all the information about a delivery. The possibility of saving all the data required for logistical control directly on the transport medium also calls for the use of rewritable RFID tags, at least on circulating transport units.

Integration offers many benefits

No matter what labeling methods are used, the results of process monitoring by auto ID are used directly for machine control and for supplying the input for product tracking. Process monitoring, track & trace, and packaging automation go hand in hand. For cost-effective, high-performance, and reliable packaging solutions with auto ID, the sensors, automation system, and user software of the packaging line must interact as an integrated, easy-to-maintain total system. Standardized system technology that includes sensor technology, SCADA, and enterprise resource planning (ERP) links and efficiently supports modular machine concepts is a basic prerequisite for this.

Several companies have been providing RFID and machine vision solutions for industrial applications in many fields for more than 25 years. A unique portfolio containing RFID, data matrix code reading systems, and machine vision, as well as control, drive, visualization, process control, and manufacturing execution systems is available and integrable into a consistent, universal system. This reduces both the complexity of the creation of new packaging machines with auto ID, optical process monitoring, and track & trace functionality and the expense of retrofitting existing packaging lines already automated with control and motion systems.

In the engineering system, the sensors are configured as intelligent I/O devices, and the details of communication on the field level and for horizontal and vertical integration are controlled by system functions of engineering systems. The direct integration of all process monitoring functions increases the performance of the entire system by using short, direct communication paths; this performance increase is immediately noticeable in high-throughput production.

Individual solutions with standard software

High reliability, short implementation times, and low validation expense are promised by packaging automation

solutions comprising pretested standard software. An example of the plug & play-capable automation of single stations and entire packaging lines is the Optimized Packaging Line concept. With standardized and easily adaptable motion-control systems, these automation solutions also meet the requirements of 21 CFR Part 11. They are based on international standards such as OMAC and Profinet and ensure harmonization of interfaces and machine operation. Software libraries are available for all important packaging jobs, including handling. They include all the necessary machine functions, from communication and operation to validated shift registers.

Guenter Lanzer, Lars Jahn

Manufacturing Execution Systems (MES): A Missing Component

Fueled by the adoption of industry standards and advances in technology, ERP is being embraced by the Life Sciences industry in this country along with the usage of the control systems at the shop floor level to automate the manufacturing process. Despite usage of such systems there is still an element of disconnect between these systems which would qualify as a component that is left unaddressed by the manufacturers. This component involves the optimization of the production process, paperless recordkeeping, real time tracking at the shop floor etc. These unmet needs are addressed through a set of solutions which are known as Manufacturing Execution Systems (MES). The following paragraphs of this article give a further perspective on the uses and the capabilities of MES.

Comprehensive Production Management

From creating master batch records for products, to executing processes consistently across manufacturing, to measuring plant productivity-MES covers all activities and requirements. MES provides manufacturers the ability to view, control and track all aspects of production on the plant floor, including materials, labels, work-in-process, equipment, work instructions, facilities, labor and documentation. The system manages these aspects through every step of the manufacturing process-from initial receipt of raw materials through weighing/ dispensing, blending and packaging activities. By guiding operators and equipment through the manufacturing process with interactive, step-by-step dialog, MES ensures that products are manufactured and packaged consistently at the lowest possible cost.

Managing Critical Data

Good MES systems provide a central repository for materials, equipment and procedural data that is very vital for the Life Sciences industry. This data from the birth of the molecule through its laboratory / bench scale to pilot and commercial scale production is managed very carefully.

MES enables flexible definition system that allows all materials, equipment and procedures to be defined. MES should also provide the standard recipe model with (General/Site and Master level recipes) with specification for Materials and Equipment at these levels. This helps in setting up newer plant taking lesser time than normal because the master data/recipe only needs to be altered to specify the new location thus making the scale up easy and less time consuming.

Product Lifecycle Management: From drug discovery to commercial production, all the data is stored and available for usage. The molecular level data is converted into the bench-scale recipe which further gives rise to pilot recipe and commercial production recipe. MES ensures data is not lost and relationship between various recipes is also maintained. It is a single source for managing the product (its specs, versions, etc) throughout its lifecycle. Workflow for internal approvals for the drug specs (since its discovery); also while transferring the recipe from bench scale to commercial scale, etc

Integration with External Systems

MES provides integration with Enterprise Resource Planning (ERP) systems, Supply Chain Planning systems, Laboratory Information Management Systems (LIMS), Document Management Systems and equipment control systems, so manufacturers gain two-way communication between the plant and the rest of enterprise. The translation of plant floor data to enterprise formats makes MES extremely valuable, not only as a system for managing the plant and leveraging your supply chain, but also for providing information to executives for smarter, faster decision making.

Integration with ERP/SCM: MES integration with business systems such as ERP/SCM aids in simplifying lots of processes. For e.g. it is possible to allow the ordering process in ERP and receiving materials against that order in MES. MES ensures to check if right qty and quality of material is received (as ordered in ERP). Integration eliminates duplicate entries and manual errors.

Suppliers can be paid based on MES feedback to ERP on the receipt of material. Thus tight integration between ERP and MES helps in improving the productivity through simplified processes.

Integration with Shop Floor Devices: MES can integrate with control systems such as PLC/DCSs via serial interface, OPC server and other available technologies. It also interfaces with Weighing scales and other analytical devices to capture real-time data via mostly serial interface. While executing, MES accepts various manual inputs/acknowledgments from operator that become part of the batch record. Thus, MES helps in providing an integrated compliance record for both manual and automated data.

MES compared with External Systems

This paragraph outlines some of the activities that is done using MES which normally is not part of the external systems like ERP, PLCs, etc.

- Direct interaction with the operator on the shop floor.
- Controls and checks manufacturing operation on real time basis.
- Convenient recipe management.
- Strong access controls and concept of electronic signatures.
- Continuously monitors the process and provides analysis for improvement.
- Eliminates errors and logs deviations.
- Enforces Good Manufacturing Practices.
- Reports deviations real-time and demands QA interactions for further processing.
- Schedules your assets and increases overall equipment effectiveness (OEE).
- Container-wise genealogy or traceability.
- Strong and effective on all regulatory guidelines and compliances.
- Streamlines finished product release on basis of quality and customer requirement.
- Generates an EBR with a special page highlighting deviations.
- Process locking in case of deviations.
- Enhances decision making power and reports Key Performance Indices' performance.

Benefits from MES

Some of the benefits that can be gained by using MES are

- Enforces compliance and reduces errors.
- Reduces validation efforts.
- Improves throughput.
- Reduces operating costs.
- Increases schedule attainment.
- Enables greater manufacturing responsiveness
- Process locking in case of deviations.

G. Anand Shankar

Manufacturing Control Systems

Integration is the key to success for Life Sciences

Inspired by the goals of optimising performance and providing paperless recordkeeping, Process Control Systems (PCS) and Manufacturing Execution Systems (MES) have improved manufacturing operations for many pharmaceutical and biotech companies worldwide. Fueled by the adoption of industry standards and advances in technology, these two systems are providing plants with a high return on investment.

Traditionally, these systems were viewed as separate entities within plants. The MES is widely regarded as an IT system because of its commercial software, servers and applications, and the PCS as an engineering function for its control and alarm monitoring capabilities.

Systems that operate independently of one another, however, are not enough to answer the evolving demands of the life sciences industry. To improve operational performance, plants require a seamless, synchronised system architecture that provides benefits such as common electronic batch records, as well as common exception reporting for automation and production management with resource traceability.

Merging PCS and MES to create a Manufacturing Control System (MCS) is an effective way to achieve these requirements, while generating a streamlined, more consistent operation. It also provides more efficient control of unit operations. For these reasons, MCS is likely to emerge in facilities as the new standard manufacturing solution by the end of the decade.

Separate systems unite

PCS as a single solution is designed to improve the productivity and profitability of industrial facilities. Batch management software, a product integrated into most PCS, provides a robust solution for designing, modelling and

automating batch processes. Using this solution, manufacturers have improved response time for production orders, as well as efficiency in meeting growing production demands.

MES, meanwhile, has proven effective in managing all steps of the production lifecycle; from specifying the materials to shipping the product. For example, leading MES systems improve manufacturing performance by controlling and tracking all aspects of production, securing predictable quality and providing a complete history for regulatory compliance.

Within the pharmaceutical and biotech industries, MES makes it easier for producers to meet regulatory compliance by managing and recording activities associated with personnel, manufacturing resources and the process itself. Additionally, the MES solution is a direct means to reduce human error during data entry. Users can reduce paperwork, improve overall resource management, and produce fully compliant, paperless production records.

From planning and scheduling to production execution, MES is able to assist production personnel in managing execution decisions. As a result, cycle times are improved, the cost of compliance is reduced and a greater responsiveness is achieved.

MES applications have matured around integrated material management and paperless plant-floor operations, which provide significant production efficiencies and cost savings. Still, personnel often must manually manage vast amounts of information. Users are required to refine production data so operations and quality decisions can be made in a timely manner.

An MCS combines the strengths of the MES for material management, manual work instruction, control and electronic batch records with the abilities of PCS technology to manage automated recipes and control unit procedures. By integrating these core strengths, MCS provides a single environment for manufacturing operations and process automation.

Close integration of the MES and PCS allows life science manufacturers to move beyond simply replicating paper tickets, "paper-on-glass" functionality and leverage all the capabilities the two systems have to offer. These capabilities include material reporting, asset management, laboratory data logging, production dispatching, Electronic Batch Record (EBR) management and electronic work instruction execution and workflows.

How it works

An MCS provides a platform for managing everything from process orders to lab results to updated inventory and lab requests. Within the unified solution, the MES interfaces with corporate-level systems such as electronic document management and enterprise resource planning applications.

The system delivers orders from the corporate-level systems down to the plant floor, and then automatically dispatches orders based on required recipes, equipment status and availability. Next, the system executes the orders within an integrated system architecture. This eliminates the traditional requirement for operators to check equipment status manually, assign equipment, load recipes and initiate batch execution, which results in fewer errors.

At most plants without an MCS, operators are assigned to manage production resources and report their status. The operator must confirm the status of specified equipment in a paper log or database before a batch can be started.

The MCS solution, however, automates this process since the programmed phase in the PCS controls specific equipment. The phase is designed to automatically request equipment and assets from the MES based on their requirement status. A transaction executed within the MES handles PCS requests for information and the MES automatically allocates resources and performs arbitration should conflicts occur. This allows the automation process to continue without interruption.

Demonstrated through MES/PCS transactions, the benefits of the unified MCS approach are evident. Unit procedural control and phase execution with an MCS is more efficient than in a traditional environment with separate system domains. Transactions between different systems and personnel are seamless; operators see a unified interface, instructions and displays.

Improved tracking and workflows

In plants with disparate MES and PCS systems, the plant operator must pull up a ticket or paper-on-glass in the MES environment to check the status of materials and verify he is adding the prescribed material. He must also acknowledge the material addition is complete and instruct the PCS to complete the execution.

With an MCS, this process is improved by allowing the PCS to interface directly with the MES, which in turn, interfaces with Manufacturing Resource Planning (MRP) as required for inventory updates. During execution of a particular phase, the system reports on the material quality, the quantity that should be added to the batch and other significant details. It then performs system data verification including tracking when the material is introduced into the batch.

When tracking material consumption, the PCS can send a transaction notifying the MES that it is time to automatically or manually consume a particular additive or ingredient. As the automated steps are processed, a procedure becomes available on the operator's screen with prompts for completing the task.

An MCS automatically presents instructions and workflows on the screen whenever they are needed, no matter the source. Operators are no longer required to coordinate with the MES activities, while staying ahead of PCS execution. This strategy revolutionises the handling of electronic instructions and workflows, eliminates paper procedures and enables a new level of plant production efficiency.

Previous paper-based systems required endless hours of collecting and reviewing paper records, reconciling

discrepancies and approving for release. Subsequent designs of disconnected MES and PCS architectures reduced the product release process to a couple of weeks. With the MCS design, it reduces this process to a few hours.

The end result

The common goal between manufacturing facilities is improved operational performance. Manufacturers seek shorter product cycle times, faster product changeover, fewer errors and better maintenance scheduling. To achieve these results, a seamless MCS architecture that provides common electronic batch records and production reporting for automation and production management with reliable traceability for materials, equipment and personnel should be installed.

By using an MCS system, pharmaceutical companies ultimately see more consistent operations between plant-level and corporate-level systems. Facility operators realise that in addition to the benefits of improved operational performance, reducing errors and ensuring compliance are critical to getting life-saving drugs to those who need them the most.

Mark Albano
Rajeev Joshi

PAT initiative speeds manufacturing, delivers consistent quality

In an effort to support innovation and efficiency in drug manufacturing, the U.S. Food and Drug Administration (FDA) introduced the Process Analytical Technology (PAT) initiative in 2003.

The PAT initiative aims to benefit the industry by supporting innovation and efficiency in the development, manufacturing and quality assurance of pharmaceuticals. Specifically, plants hope to see results by reducing production cycle times; preventing rejects, scrap and reprocessing of materials; increasing automation to improve operator safety and reduce human errors; and enabling real-time release.

Much of the initial work with PAT has focused on the development and application of analytical devices for timely measurements; however, it is only one aspect of the initiative. To fully address PAT's goal of achieving complete understanding and control of the manufacturing process, a wider variety of tools must be applied.

To integrate PAT into the overall scheme of process control and automation, there are various types of tools the FDA has identified, including:

- Multivariate tools for design, data acquisition and analysis
- Process analyzers
- Process control tools
- Continuous improvement and knowledge management tools

Using these tools allows manufacturers to focus on the five key elements of manufacturing: people, materials, facilities, equipment and documentation.

Additionally, by integrating these tools into the process control system, benefits such as faster development of new products, shorter manufacturing cycle times, higher yields, reduced waste materials, and fewer product recalls will be realized.

Successful Tools for PAT

The foundation for the use of multivariate tools for design, and analysis leading to process improvement is reliable data. Industry tools are available that collect, store and replay historical plant process data. This makes timely information visible at the production level and throughout the enterprise. Access to timely data empowers plant staff to better align, plan, execute and improve business performance, which increases efficiency and translates to the overall goal of the PAT initiative.

With a foundation of reliable process data, multivariate analysis tools can be applied effectively. When selecting a multivariate tool, it's important to consider two factors: its ability to continuously monitor and quickly detect impending abnormal situations, and its ability to localize and identify the root cause of the impending events to allow a measured and appropriate response. It can be used for root cause analysis and the development of statistical models that identify cause and affect relationships to improve process understanding. Equally important, these models can be applied as part of a PAT control strategy to improve manufacturing performance by avoiding abnormal situations and reducing human errors.

Another tool that lends to the overall goal of PAT is the process analyzer. Process analyzers provide proven measurement and control solutions to keep plant operations running smoothly, efficiently and safely. An example of a process analyzer is the Laser Induced Fluorescence (LIF) sensor, a non-invasive device used to determine the homogeneity of dry powder blends.

The benefits of using an LIF correspond directly with the basis of the PAT initiative. This specific tool reduces the cycle time by eliminating off-line analysis and by defining a real end point that can be measured online. Quality assurance is also tracked through use of the LIF as well as rapid analysis.

Process control tools are an important element of a PAT solution. Process control tools help collect, synthesize and share process and business knowledge from multiple sources across the enterprise, and recommend appropriate actions so operators can increase their productivity. A more consistent operation through the application of automated control strategies, helps to prevent rejects and reduce human error.

Improvements to alarm system design can also lead to improved operator efficiency and decrease the amount of possible process upsets. Alarm management solutions help ensure that alarm systems perform effectively to protect uptime and safety operations by allowing operators to detect and correct process faults at an early stage. Other alarm management tools support PAT by offering functions that provide metrics of events and process history for root cause analysis of abnormal situations. Features that separate automatic notifications as low-priority alarms from true alarms are also valuable to alarm management. This feature permits the alarm system and operator to focus on alarms requiring immediate action.

These tools mentioned above are critical to ensuring that collected data are relevant and representative of process and product attributes, and allows the operator to be more effective. They directly address the reasons why the FDA launched PAT, to help the drug industry deliver higher quality products and improve the manufacturing process.

Mark Albano

Tablet Press Monitoring System

Key Features

- Production Speed @ 5,000 tablets per minute
- Measurement and decision speed: 12msec per tablet
- Counts total number of accepted and rejected tablets
- Multiple turret selection of different sizes and shapes and detection of minor variations in object formulation
- Statistical Analysis of force data
- Low False Rejection Ratio
- 100% Quality Control
- 21CFR Part11 Validation Compliance

Tablet Press Settings Optimized by Instrumentation

Tablet Hardness is directly proportional to Thickness & Hydraulic/Spring Pressure. In some cases, excess pressure can make the tablets brittle and hardness can go down. Thus, the behavioral pattern can be ascertained for the longer life of machine and better product for the customer eventually.

Load Cells are fitted in on Compression Roller Bearings & at Ejection Point. Newton's Third Law is applied in this system. When the upper punch & lower punch comes between upper pressure roll & lower pressure roll, granules are compressed. The compression force generated on the granules also causes Reaction Force towards the Pressure Rolls. This Reaction force is being measured by Load Cells. Load Cells signals acquired by a data input card are scaled with real world units and are compared with the set limits. If the actual value not falls under set limits, system starts indexing that particular object and the same will rejected at desired location using high speed Air solenoid. All statistical data and Set point limits are communicated with SCADA through TCP/IP at regular interval for history and further downward analysis.

System Flow

The functionality of the Tablet Press System can be divided into 2 main tasks:

High Speed Data Acquisition & Monitoring High Speed data acquisition & monitoring of average peak value of Load Cells at every revolution Main Compression, Pre Compression, Ejection Force, Punch Tightness Top and Punch Tightness Bottom Load Cells data are acquired on each encoder pulse edge which is related to physical angle of turret in resolution of 0.1 degree. So actual number of data points are equal to number of encoder pulses per revolution. Once filtering and offset is applied, data analysis is carried out. Per revolution average peak for each Load Cell and standard deviation for Main Compression force is calculated from analyzed data. Row value, average peak value and standard deviation are sent to SCADA continuously.

Rejection of Tablet if Main Compression Peak Value is out of Set Limits on Every Punch On the Punch Signal, set limits are checked with peak value of Main Compression Load Cell and accordingly bad tablets are rejected after indexing. Air Solenoid for rejection becomes on after wait time and pulse is generated based on Solenoid on time. Reject counter indicates total count of rejected tablets. Counter Reset command from SCADA resets the reject counter. Reject punch shows actual punch number from which tablet is rejected. This helps to identify if tablet is rejected from the same punch repeatedly.

The last revolution total peaks data of Main Compression Force are sent to SCADA on request.

Real time simultaneous loops running parallel are required to meet measurement and control action simultaneously. At the same time, real time connectivity on TCP/IP for further SCADA integration is required. Optimized level of programming provides a complete solution to the customer fulfilling all the requirements & functionality.

Conclusion

An Instrumented Tablet Press gives correct & precise data on Main Compression Force, Pre Compression Force & Ejection Force. This data when plotted on chart helps a pharmacist to understand the peculiar behaviors of a Tablet more precisely and arrive at conclusions like what should be the Tablet Press settings, formulation, etc.

One can measure the impact of variation in the Tablet Weight by depth of fill adjustment in the Tablet Press, Tablet Thickness by adjusting the main compression (Gap between Upper Punch Tip & Lower Punch Tip) and Tablet Hardness / Thickness by adjusting hydraulic pressure / spring pressure.

Thus, Tablet Press Monitoring can be successfully utilized in Quality Control, Formulation Development and Formulation Analysis.

Himanshu Bhavsar

The AIA Newsletter is published by the Automation Industry Association. We welcome your feedback and requests for any further information.

Registered Office: Plot No. 22A, Shah Industrial Estate, Off Veera Desai Road, Andheri (West), Mumbai 400 053
Editorial Office: B-404, Ansal Chambers-1, 3 Bhikaji Cama Place, New Delhi 110066. Ph: 011-41659981
www.aia-india.org email: aiateam@gmail.com

Designed and printed by stetdelhi@gmail.com