# Manufacturing Execution Systems to Optimize the Pharmaceutical Supply Chain

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**Abstract**

Manufacturing Execution Systems (MES) enable the pharmaceutical industry to reduce production costs and increase compliance with regulatory requirements significantly. This is due to the capability of an MES to optimize business processes in the production supply chain, improve product quality and ensure the safety of manufacturing processes.

This article provides practical advice on how to make the implementation of an MES solution a success story. The article examines various production architectures and the associated process workflows and states criteria to determine benefits and functional scope of an MES. The required functions and interfaces are listed and implementation strategies are introduced. Finally case studies describe successfully installed MES systems and document the benefits achieved for the users.

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Rolf Blumenthal has been working with Werum since 1979 and is one of the 15 employees who took over the company after the death of the company founder Wulf Werum in 1982. He has gained outstanding expertise in the management of large-scale and international MES software projects for Pharma and Biotech industries.

For more than five years Rolf Blumenthal has managed the product development for Werum's MES software suite PAS-X. In this context, compliance with GMP and FDA requirements is of prime importance. Since PAS-X is operated as an Electronic Batch Recording System in the pharmaceutical industry the guidelines of the GAMP Community are of particular relevance for the product development process.

Since Rolf Blumenthal is a renowned industry expert with hands-on experience and comprehensive technical expertise he started international consulting activities in 2005. In this role he advises PAS-X customers on the following major topics: IT architectural blueprints, system integration, computer system validation, optimized use of PAS-X, and efficient creation of master batch record libraries.

Rolf Blumenthal is a member of the GAMP D-A-CH Forum where he is actively participating as editor and reviewer of new guidelines. Since 2002 he has been a member of the GAMP D-A-CH Steering Committee and of the Special Interest Group "Validation of Small Manufacturing and Weighing Devices".

## Contents

# 1 Introduction

As a production manager or having a similar position in the pharmaceutical industry you might be familiar with a setting like this: Long rows of files with paper documents, some of them still partly unprocessed; colleagues constantly asking you "What do I have to do next"; and not to forget the permanent discussions with the sales department on which products are required urgently tomorrow.

Would you not prefer a situation like this: your personnel is equipped with RF hand-held terminals and can inquire the activities next in line at any place and at any time; your operators thus execute the required activities as specified. And on top: a complete, electronic documentation and a statement about the performance and status of your production and packaging upon the click of a button.

A Manufacturing Execution System (MES) is at the core of such a scenario. An MES controls, optimizes, and documents business processes executed on the shop floor in full compliance with all the pharmaceutical requirements. It is the goal of an MES to increase security and reliability of the manufacturing process and to improve product quality. MES solutions are suitable for different processes including chemical or biochemical manufacturing of active pharmaceutical ingredients as well as the subsequent processing of such APIs in solid and liquid pharmaceutical forms.

MES solutions are not isolated but a core component of the entire supply chain IT architecture. In 1998, AMR created the REPAC Model (Ready, Execute, Process Control, Analyze, Co-ordinate) and thus laid the foundations for the basic understanding of the necessity to use an MES. An autonomous MES enables the support and optimization of business processes by means of software functions. To actually achieve such potentials and optimize the IT architecture on the long run, it is necessary to standardize the functions and workflows in logical units. Typical examples of such a view are Weighing & Dispensing, Electronic Batch Recording, Equipment Management, Deviation Management with CAPA functions (Corrective Actions / Preventive Actions).
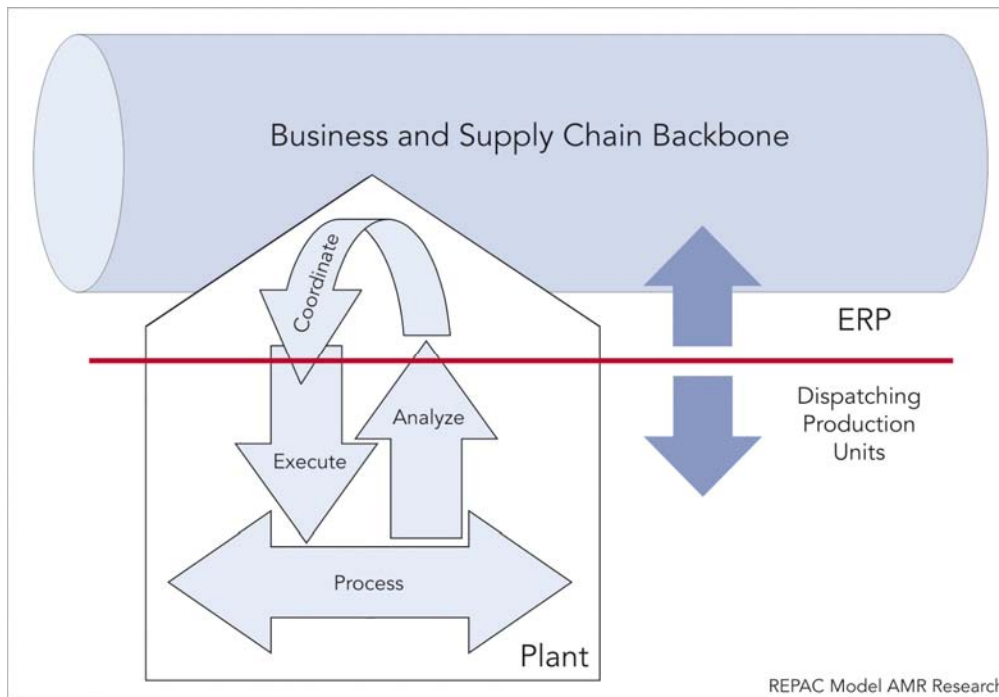
**Figure 1: The REPAC model (Ready, Execute, Process Control, Analyze, Coordinate)
laid the foundations for an MES (source: AMR)**

A Manufacturing Execution System is an electronic interface between personnel, equipment automation, orders, logistics, equipment and processing instructions (batch records). Thus, the MES is located between the company-wide Enterprise Resource Planning System (EPR) and the process control systems (DCS). The MES mediates between business administration (covering core functions such as sales and production planning or controlling) and the automation of the production process.

## 2 What are the Benefits of an MES System?

The implementation of a complex MES solution involves large investments. Therefore, some questions have to be answered to justify these costs. How can the user determine the necessity of an MES and how does the user benefit from an MES? Only measurable and quantifiable advantages can provide an economic investment justification.

In this context, a systematical procedural approach is essential. Objectives have to be defined and typical characteristics of the examined plant and the involved business processes have to be analyzed. The information obtained in such a matter is a solid basis for an objective assessment of the benefits provided by an MES.

However, despite the importance of such a structured approach it cannot be denied that the decision for or against the benefits of an MES system frequently involve factors that are not measurable in economic terms.

### 2.1 Objectives

Typical goals to be achieved by the implementation of an MES system are:

- Optimizing of the entire supply chain with the MES system best suitable for controlling workflows and procedures
- Improving process safety and reliability
- Recognition of deviations at an early stage
- Immediate documentation of process steps
- Improved data quality for assessing processes and products
- Visibility and transparency throughout the entire production process: only deviations are to be analyzed, a detailed examination of the normal flow of operations is no longer required
- Reduction of storage costs due to reduced lead times (WIP)
- Reduction of administrative work for maintaining manufacturing documents
- Creating and approving master batch records
- Reducing the number of lost batches
- Reduction of operating costs due to a high level of integration and thus prevention of isolated solutions
- Rapid access to current data: management based on up-to-the-minute information for all critical business cases
- Complete 21 CFR Part 11 compliance also for lower-level systems

## 2.2 Various Production Architectures

In pharmaceutical production there are typical production structures for manufacturing active pharmaceutical ingredients or dosage forms such as tablets, ointments or liquids. These structures can be classified according to specific criteria. This classification can be used to define the different benefits levels of an MES for a particular production architecture in detail and by degrees.

Moreover, such a classification also leads to different implementation concepts for an MES system. It would be wrong to claim that there is one software solution to provide optimal support for the respective type of production.

Obviously, such structures can only be regarded in a rather abstract way. Thus, in concrete cases there may be deviations from the general patterns. For this reason, it is always advisable to analyze a concrete example.

In this article, we only consider **regulated** production areas operating on the basis of master batch records. The examples we use refer to the biopharmaceutical production of active pharmaceutical ingredients and the production of solids. Similar structural descriptions could be established for the production types we cannot regard in this paper.

## 2.2.1 Architectural Design of Biopharmaceutical Production

Biopharmaceutical production of active pharmaceutical ingredients is characterized by natural fermentation processes of germs. Depending on the progress of the process the results of a previous phase have to be distributed onto additional equipment that is getting larger with every step.
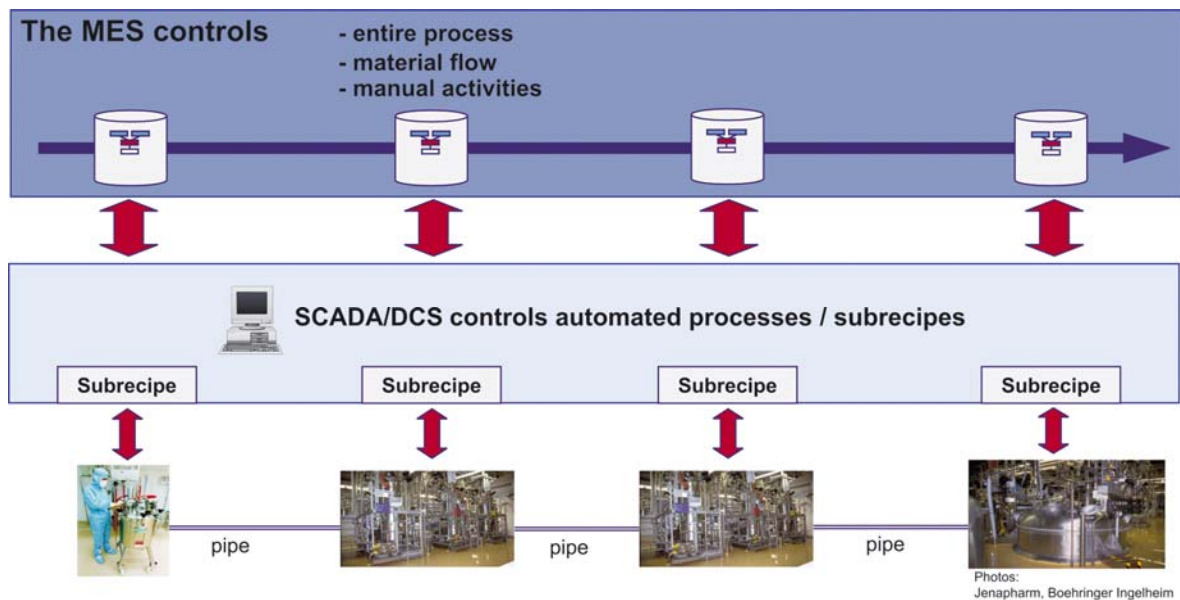
**Figure 2: Biopharmaceutical API production – principle structure**

Characteristic features of biopharmaceutical production:

- Highly automated production

- Sub recipe control by means of a DCS

- Few manual material transports

- The process is running "on rails" with just a few buffering possibilities

- Production requires a reliable verification of the cleaning status of all the different equipment

- Equipment management

### 2.2.2 Architectural Design of the Production of Pharmaceutical Dosage Forms

One of the characteristics of the production of pharmaceutical dosage forms is the material flow using containers. The master batch records states fixed batch size limits related to the container size. The input material quantities and the further operations are based on these limits.

Following the weighing/dispensing of material into a container it is transported from work centre to work centre where it is processed according to specification. Sometimes the production workflow

in the building involves several floors. Some containers are transported in lifts and in some cases the force of gravitation facilitates material transfer.
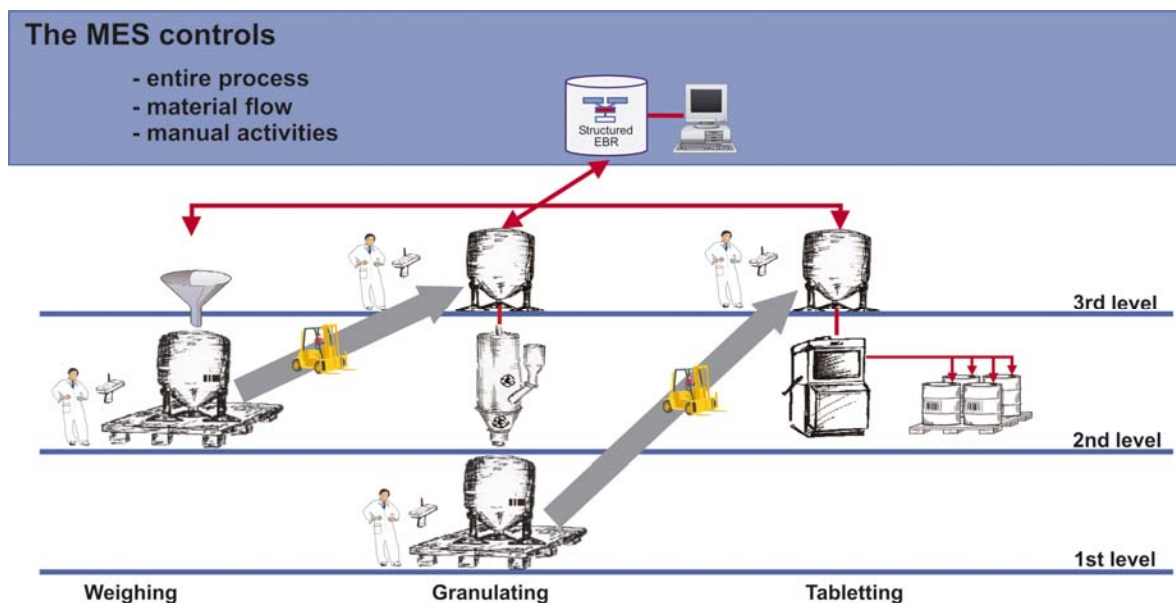


**Figure 3: Production of pharmaceutical dosage forms – principle structure**

Characteristic features of a manufacturing process for pharmaceutical dosage forms:

- A large number of work centers
    - 5-10 granulators
    - 20-40 tabletting machines
    - 10-20 packaging lines
- The individual work centers are located in isolated workrooms with controlled access to ensure GMP-compliance
- Many manual material transports in containers
(The process can be interrupted and WIP material can be held for further processes)
- Various, independent and few complex SCADA systems controlling individual machinery
- Material can be added and/or further processes be initiated on several production floors
- Vertical transports across the levels
(i.e. it is necessary to check that the correct containers are placed at the correct machines)

One of the major utilities for process acquisition and control are mobile RF terminals and barcode scanners. They enable the identification of objects (such as containers, workroom or scale) at any location, provided that these objects are equipped with a barcode label.

## 2.3　Classification and Assessment

It is possible to use a criteria catalogue to clarify in how far an MES solution in a production plant provides benefits for the user or not. The checking of the criteria enables a judgment on the concrete case. The following list states some of the criteria to be used for assessment.

- Type of process equipment
- Complexity of products
- Degree of automation in production
- Transports using containers
- Information about equipment status
- Work required to document production
- Material inventory in production (WIP)
- In-process control operations

One tendency is recognizable: the benefits in the supply chain increase from API production towards packaging.
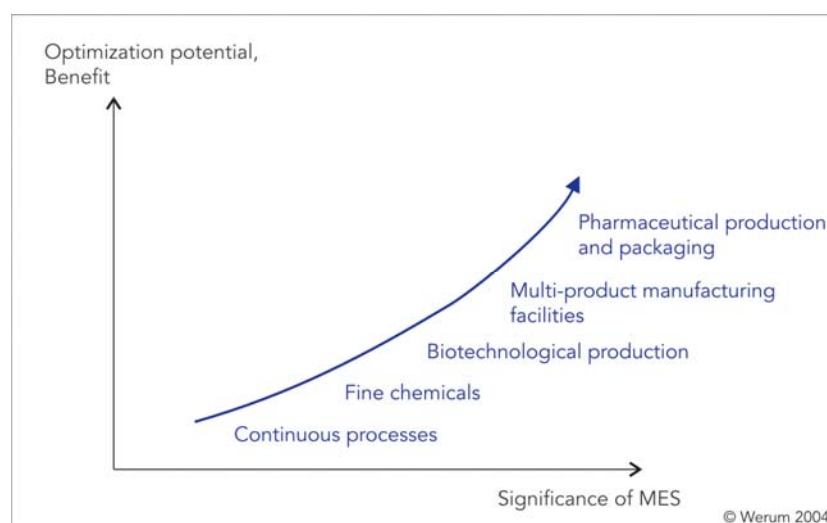


**Figure 4: Significance and benefits of MES for various production structures**

## 3 Positioning within IT environment

In the production supply chain it is the MES systems that substantially contribute to vertical integration. All the individual systems of a company, the ERP system as well as the systems on plant operations level down to the equipment merge into one overall system. In the context of integration, the state of the art achieved by now provides good technical safety if adhering to standards like ISO S95, ISO S88, or Namur NA 94. Solutions for individual industry segments are developed, which require only reduced development efforts and implementation times.

How are the required functionalities to be distributed to the involved systems? This is a question frequently discussed when an enterprise plans to implement an MES system. The distribution of functions to various systems which support the individual task in the best possible way is a common task and can be solved without major problems. However, it is not only necessary to distribute the data but also to define which system is primarily managing the respective data. A system has the sovereignty over data if it originally produces the data and transfers it to another system for further processing. A material master, for instance, should originate in an ERP system and should also be maintained and processed there. An MES, though, may add attributes and data to make sure that pharmaceutical aspects are considered in the best possible way.

The ISA standard S95 focuses on the aspect of integration into IT environments. The descriptions given in the standard provide a suitable basis for settling questions relating to task distribution and interfaces.

### 3.1 Overview of Standards ISA S95.00.01/02/03

The standard ISA S95 consists of three individual parts:

- Part 1 defines models for describing the distribution of tasks between ERP and MES systems (ISA-95.00.01) [1]
- Part 2 describes the associated data models (ISA-95.00.02) [2]
- Part 3 defines a catalogue of functions  (ISA-95.00.03) [3]

The standard describes those areas on enterprise and plant operations level that deal with any kind of activity required to manufacture a product and to control this process.

The first part of this standard with its description of the interface between ERP and MES may help to position an MES system. In a first step, the standard divides the organizational structure into four levels, with the ERP systems on level 4, the MES system on level 3 and the equipment interfaces on levels 2 and 1.
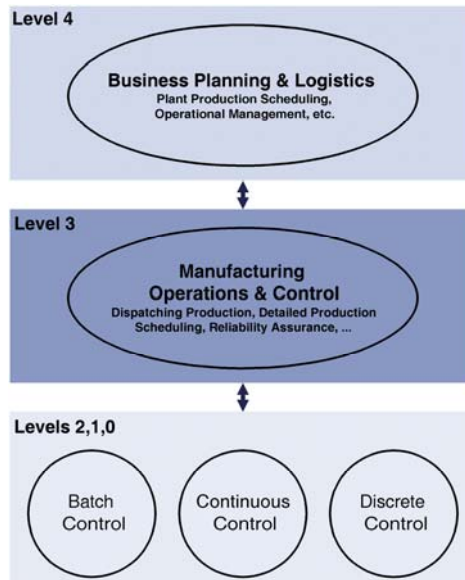
**Figure 5: ISA S95 level concept**

An additional, more detailed model description illustrates the data flow between the functions for production plants.
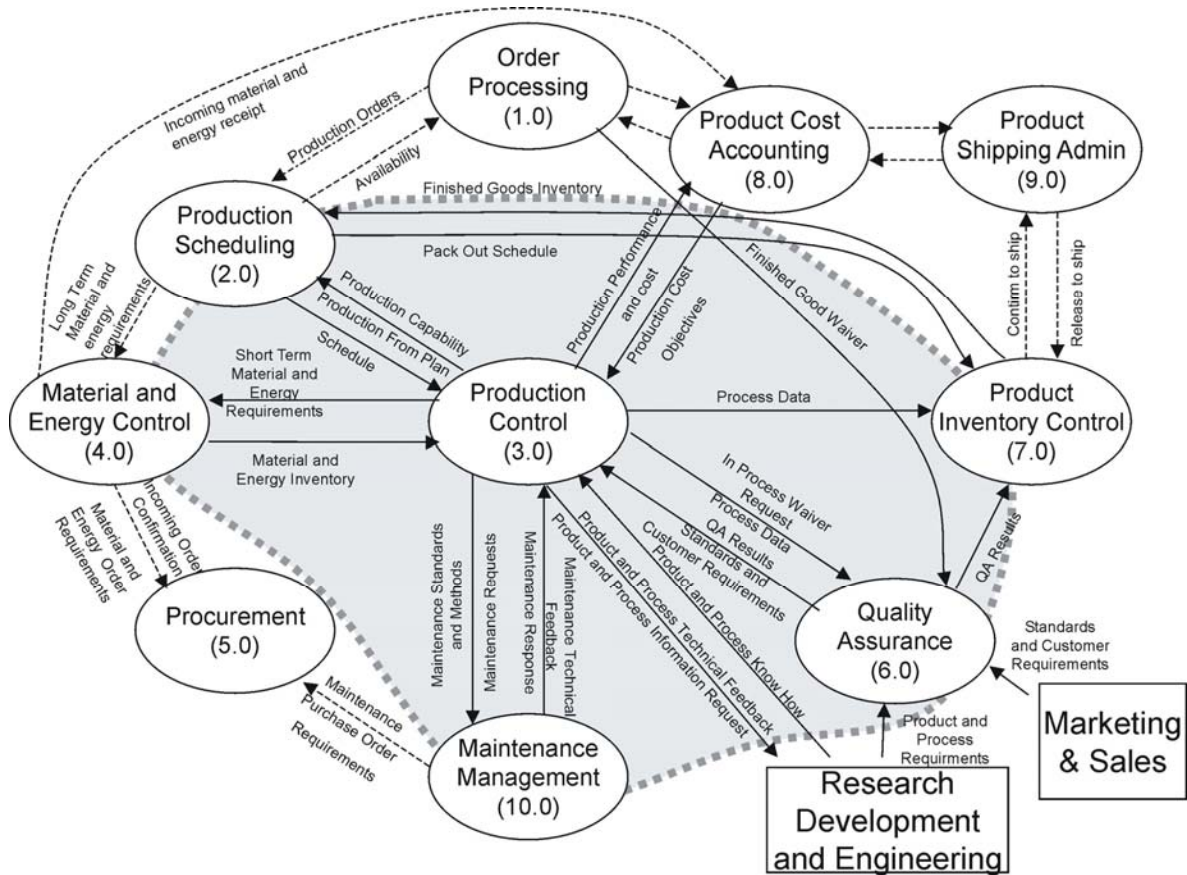
**Figure 6: Scope of enterprise-control integration**

The dotted lines define the interface between levels 3 and 4. The arrows show the flow of data between the levels.

## 3.2 ISA-Compliant MES Integration

### 3.2.1 Integration with an ERP System

Following the specifications of ISA S95 the pharmaceutically relevant data are to be handled by the MES system when the MES and EPR system are integrated:

For this reason, level 3 comprises the functions

- required to maintain "regulatory compliance"
- adding to the reliability of plant operations
- relating to the required equipment
- required to enable supervisor to control plant operations



**Figure 7: ISA-compliant distribution of functions between ERP and MES system**

### 3.2.2 Equipment Integration

Equipment interfacing by means of PLCs enables the MES system to use automatically acquired data. Such data are more reliable than manually collected data, since errors during manual data entry can be ruled out.

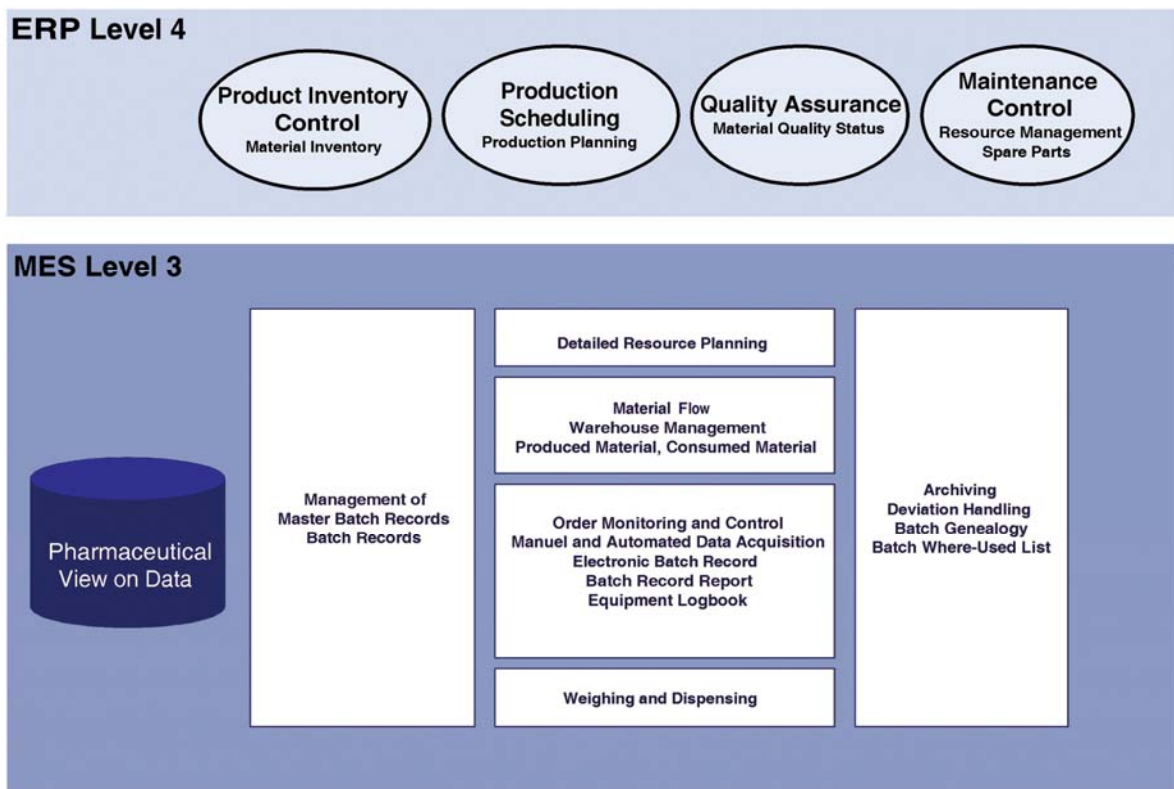On the other hand, equipment interfacing involves some effort for integration and qualification. Once such a system is running and validated, MES users can add originally acquired operating data or rather sophisticated conversions to their batch records.

The MES collects such operating data in a production database (Historian Database) and places relevant data available for the manufacturing report. The production database enables all kinds of analysis which may also involve further data of the MES.

Operating data (such as temperature, pressure, or alarms) can be acquired by DCS systems for process control as well as by SCADA systems for machine visualization, PLCs for machine control, or by manual data input. Online queries are possible at each process step. Due to a time stamp and the batch time frame (start/end of batch) the data are assigned to a produced batch.

The interface requires special attention if a DCS system is used to integrate equipment which at the same time presents a recipe-driven batch system. In this case, **pharmaceutical master batch records** and **process recipes** have to be harmonized. As both the master batch records as well as the recipes are hierarchically structured descriptions, there should be a level on which the descriptions can be mapped.

Also in this context the ISA standards S95 and S88 [4] [5] are a good help. On MES level, the master batch records take into account the entire plant with all its workrooms and even the individual machines (units). The process recipes, on the other hand, consider all phases and technical functions of the machines and subsystems down to the individual acquisition values and control elements.
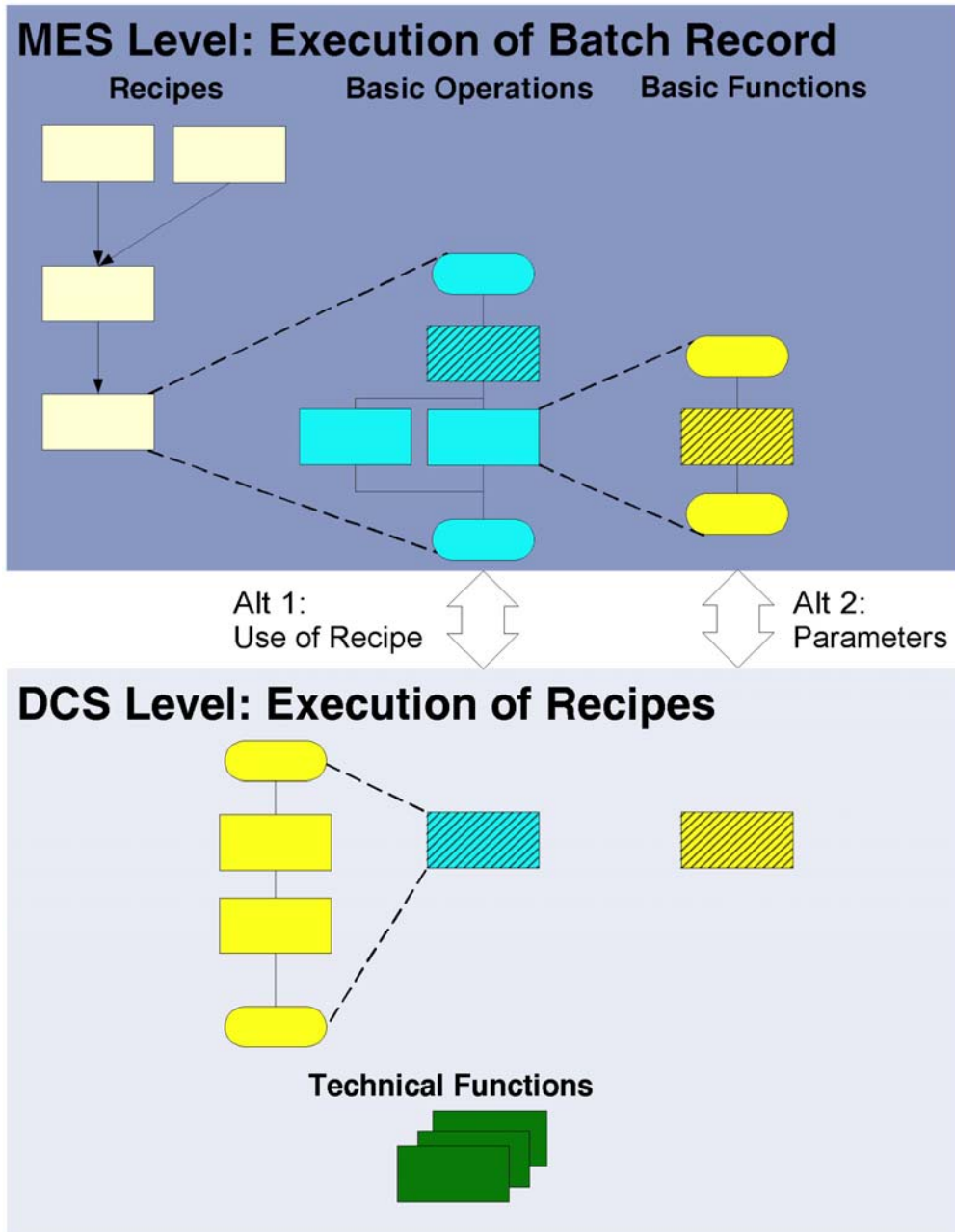
**Figure 8: MES and DCS system: Recipe integration**

# 4 Functional Packages

On MES level 3, the standard S95 positions the complete functional package "Production Operations" and parts of the functional packages "Material Inventory Control", "Quality Assurance", and "Maintenance Management". Considering the integration layers you get the following structure for an MES system:
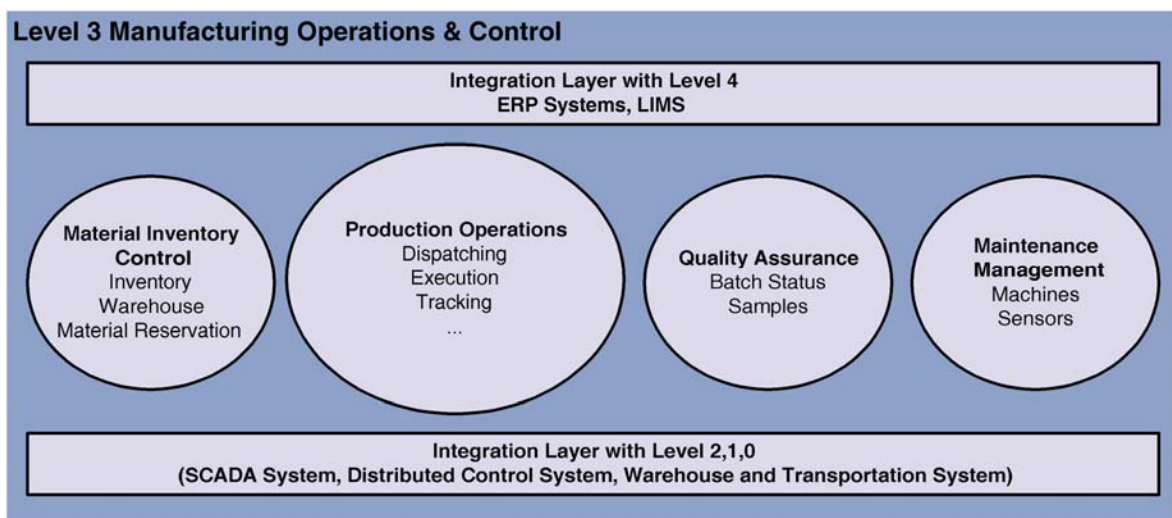


**Figure 9: Components of an MES system**

The component "Production Operations" comprises four main sets of functions defined for the following tasks:

- Definition of production

- Management of resources

- Planning and execution of product manufacturing

- Acquisition, documentation, and analysis of production

Further detailing divides each functional package into a number of function groups:
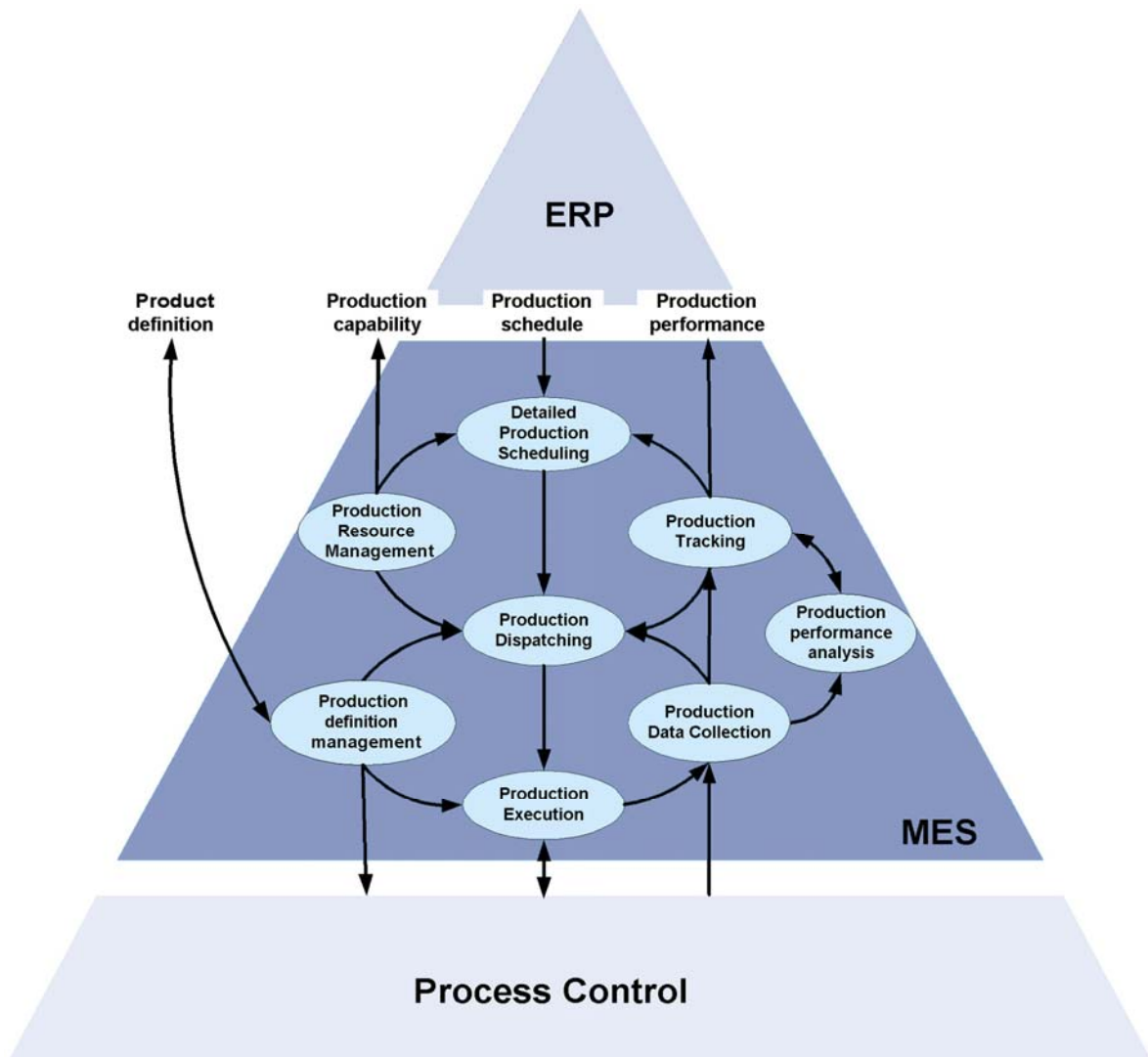


**Figure 10: Function groups of the package "Production Operations"**

## 4.1  Functions Required on MES Level

**Product definition management:**

- Additional material master data
- Definition of master batch record
- Bill of material
- Operations
- Material flow in production
- Review and approval workflow
- Management of versions

**Production resource management:**

- Management of personnel and consideration of proper certification
- Equipment management, e.g. container, scales, tanks, setup parts, workrooms
- Management of  material resources
- Coordination with maintenance management
- Management of future resource capabilities
- Equipment management, ensuring the right status for usage (like cleaned, in use, calibration required)
- Electronic logbooks

**Detailed production scheduling:**

- Allocation of shop floor orders to machines
- Comparison between actual and scheduled production
- Monitoring of work centers and resources
- Monitoring of order statuses

**Production dispatching:**

- Allocation of resources (personnel, equipment, material) to manufacturing orders -> shop floor orders
- Starting, stopping, interrupting and resuming of production order
- Batch record execution
- Performing assigned procedures and activities
- Reacting to deviations
- Throwing exceptions
- Taking samples
- Review and approval of batch record

**Production data collection:**

- Manual data acquisition
- Automated data acquisition
- Weighing and dispensing using scales
- Calculation of new values based on formulas
- Storing of production data in event or time context (trends)
- Acquisition of deviations, events and alarms

**Production tracking:**

- Electronic batch record report
- Batch genealogy
- Batch where-used list
- Deviation handling
- Tracking of all material movements
- Process analysis
- Statistical process control
- Production performance analysis (KPIs, e.g. cycle times, resource utilization, equipment utilization)

## 5 Regulatory Requirements

Depending on the country the products are delivered to, an MES system for the pharmaceutical industry must **functionally** comply with the requirements of regulatory authorities in Europe and/or in the United States:

- GMP requirements of FDA (21 CFR Part 210/211) [8]

- FDA requirements (21 CFR Part 11) for electronic records, electronic signatures [9]

These regulations for instance define the procedure for identifying a container (21 CFR Part 211.80 and 105) or the requirements electronic signatures have to meet (21 CFR Part 11.100-300).

Beyond this, there are a number of requirements and guidelines by regulatory authorities stating the **QA procedures** relating to the Software Development Life Cycle in order to guarantee software products of high quality. Examples are:

- GMP guidelines of EU [10] [11]

- GAMP 4 guidelines [12]

European and US laws may vary in details; what they have in common is the requirement for the validation of computerized systems. The fundamental prerequisite that qualifies any system for validation is that clearly defined QA policies have been observed throughout all project phases.

In this context, the GAMP V-model has become generally accepted in the pharmaceutical industry. The V-model divides the production and maintenance of software systems into the phases Design Qualification, Development Implementation, Factory and Site Acceptance Test, Installation Qualification (IQ), Operational Qualification (OQ), Performance Qualification (PQ), and Ongoing Qualification.

All these phases have to be concluded with a verification to prove that all the requirements for the respective phase have been fulfilled. All the verifications have to be performed in a formal and systematic way. Change management procedures have to be established to ensure an overall consistency of the entire documentation across all phases.

**The computer system must be developed and tested in accordance with a quality management system. In the pharmaceutical industry software lacking appropriate proof of such QM compliance is hardly acceptable.**

## 6  Implementation Strategy

Since an MES system considerably affects production processes and their documentation, detailed planning is required to make its installation a success. After all, established, reliable procedures using paper are substituted by electronic procedures. Especially, if an MES system entirely replaces the production documentation on paper by Electronic Batch Recording, all possible risks have to be analyzed and ruled out. This is because one thing is for sure: a batch without documentation cannot be sold.

In order to minimize the risks and gain the customer's confidence by first installing a smaller system of manageable proportions the following recommendations should be considered:

- **Implementation in phases**

  The implementation should be carried out in phases. In a **pilot phase** an existing, operational standard system (MES product) demonstrates the functions that are available or missing in the implementation. The findings can then be considered as improvement in the next phase, the **implementation phase**. Such improvements may not only concern the software but also the workflows. The resulting system is already adjusted and suitable for productive operation in a plant. In every-day use further requests for improvements may come up. An overall picture of the customer's standard system will finally turn out by including further requirements made by other plants.

  Such additional functions can be integrated in a roll-out version of the software product. During the **roll-out phase** a proven, familiar system is available to the customer, which can also be transferred to other sites with only little effort (saving up to 50 %).

- **Integration of all key users**

  The best system will not be accepted if the users do not get the opportunity to get familiar with the system before it is actually implemented. Unless key users get the necessary experience in handling the new system and an understanding of the objectives to be achieved by installing this system, the management will run the risk of loosing the users' support. The implementation would inevitably be doomed to failure.

  For this reason, the key users should be integrated at a very early stage, for instance when defining the system requirements or when analyzing the functionalities. As soon as the pilot system is available, training courses should be held. In this phase, **key users are just the right persons to make crucial contributions to improving** the system or supported workflows. It is important to win the key users and make them advocates of "their" system. They have to be convinced of the benefits the MES provides for them.

- **Focusing on sophisticated system configuration and customization**

As MES systems are supposed to be flexible enough to adjust to the most versatile workflows, customization is necessary and wanted. This applies in particular to EBR functions since their scope is strongly influenced by parameters set for the master batch record. It is to be noted that depending on the complexity of procedures and the number of products to be manufactured, customization activities lasting up to several months are not uncommon.

In general, master batch records exist on paper already and their contents are known. But effective operation of an MES is related to the availability of well-structured master batch records in the system. They are essential to profit from advantages as provided by predefined building blocks. **Reusable description elements are a core factor in reducing the effort for creating master batch records** considerably and consistently. The required restructuring of data existing on paper represents an intellectual challenge that should not be underestimated. The best way to solve the problem is to integrate process engineers, who are well-trained in defining master batch records, right from the start phase of the project.

# 7  Case Studies

## 7.1  Production of Pharmaceutical Solids - Bayer Health Care

Bayer HealthCare, a subgroup of Bayer AG, is one of the world's leading companies in the health care and medical products industry, combining the global activities of its Animal Health, Biological Products, Consumer Care, Diagnostics and Pharmaceuticals divisions More than 34,000 employees work for Bayer HealthCare worldwide.

Bayer HealthCare's Pharmaceuticals Division develops innovative and highly effective drug products. The research programs cover life-threatening conditions but also disorders that markedly impair quality of life and life expectancy. The division has a promising early product pipeline, in particular for the indications cancer, cardiovascular, metabolic disorders, and anti-invectives.

Each year several billions of tablets leave Bayer's manufacturing facilities for pharmaceutical solids in Leverkusen. Such highly sophisticated production facilities demand software-based support during all phases of production to ensure that patients get a drug of stable quality.

### 7.1.1 Purchased Software to Profit from the Experience of Other Users

Bayer started looking for a manufacturing execution system that offered the "customary comfort", met today's and tomorrow's GMP compliance requirements and was apt to support optimal material flow control, reliable user guidance and paperless production with electronic signatures. At first, Bayer was not sure whether to use in-house development or purchase a market software package. Based on the argument that with a purchased software package you can indirectly benefit from the experience of other users they finally decided in favor of the MES system PAS-X

PHARMA by Werum Software & Systems.

### 7.1.2 A Focus on Flexible Processes

Bayer was looking for software that can be configured in a simple way, that enables them to create recipes easily and which has a flexible structure. This is essential since the manufacturing of solid pharmaceuticals is characterized by a large number of recipe variants. Several hundred recipes are not uncommon. Thus, the administration and creation of Master Batch Records with all relevant order and batch data is one the system's core functions.

With the objective to obtain high throughput and productivity the recipes are structured so that they may be executed on different machines. It must be possible to switch between different equipment without any problem.

A change of equipment required while the process is running is a real challenge, and fortunately only happens rarely. Any modification of the batch record needs to be visible in the documentation, but any impact on the Master Batch Record has to be avoided.

Also during "normal" batch record execution the collected data are continuously compared to the stored recipe. The next step can only be initiated if all the data match. Such verifications are automatically performed by the system. The entire workflow with all the associated deviations is electronically documented, and then finally evaluated. This way safety procedures are integrated into the process, and it is ensured that all the workflows are correct.

Transparency was also requested for the mapping and control of the complex material flow. It was one of the primary goals to enable an easier and safe way of identifying the products across the entire production process.

### 7.1.3 The Reality of Electronic Documentation

Meanwhile, a fourth partial goal has been achieved. Apart from a few forms, paper has completely disappeared from production. All documents only exist in electronic form. Also all the signatures required for the approval of individual production steps are performed electronically. It is ensured that documentation and signatures are 21 CFR Part 11-compliant.

### 7.1.4 Integrated Systems

The Manufacturing Execution System is integrated into a comprehensive IT framework concept. At the level above, there is a Unix-based system supporting materials planning, order creation and the entire supervisory control planning. Below the MES, there is the machine level to which the MES offers standard integration modules. A standard interface has been implemented to SAP. It ensures that all pharmaceutically relevant data remain in the Manufacturing Execution System. Material inventories are administered in SAP. Another important feature: the Manufacturing

Execution System provides an automatic master data interface to the SAP system. In case recipes are changed in the MES the interface makes sure that the master data are automatically reconciled between MES and SAP.

### 7.1.5 Wrap-up

Looking back on more than four years of practical experience with the Manufacturing Execution System Bayer strikes a positive balance. Following an initial phase of familiarization, the user satisfaction was complete. The use of mobile RF terminals has proven a real success. The operators truly welcome the high degree of mobility and the safe guidance guaranteed during the execution of orders.

In using the MES, Bayer has been able to further optimize pharmaceutical safety, to substantially increase the transparency of the material flow, and to implement measures for boosting efficiency of the manufacturing process.

### 7.2    Biotechnical Production - Boehringer Ingelheim

Boehringer Ingelheim is a research-driven group of companies dedicated to researching, developing, manufacturing and marketing pharmaceuticals that improve health and quality of life. With more than 34,000 employees and 152 affiliated companies spread all over the globe, the company's two core businesses are Human Pharmaceuticals and Animal Health. The former is made up of the business segments Prescription Medicines, Consumer Health Care and Industrial Consumer, which includes Chemicals and Biopharmaceuticals.

At the locations in Biberach (Germany) and Vienna (Austria), Boehringer Ingelheim can provide the entire biopharmaceutical process chain from genetic cell development to large-scale commercial manufacturing.

### 7.2.1 Biotechnological Requirements

The demands in biopharmaceutical production of active pharmaceutical ingredients (API) are particularly high. In the new API facility Boehringer Ingelheim will produce highly innovative biopharmaceuticals. These advanced products are the result of many years of extensive pharmaceutical research and, without a doubt, represent cutting-edge performance in pharmaceutical production skills. A vital contribution to this process is the MES system by Werum, which has been tailored to meet the very specific requirements of biotechnological production.

Over the last years, no other project in Europe's pharmaceutical industry has gained as much notice as the new active ingredient plant of Boehringer Ingelheim in Biberach, Germany. As the largest cell culture plant in Europe, it set a new record in development and construction, and currently surpasses all others in terms of technology. In less than three years, more than Euro 255 million has been invested in this biotech complex. Just imagine: more than 18,000 cubic meters of

concrete, 2,700 tons of steel, 600 huge biotech apparatuses, 70 kilometers of piping, and about 800 kilometers of cable were used in the construction of the building.

### 7.2.2 Coordinating Complex Processes Safely

Without a Manufacturing Execution System that interfaces closely with the distributed control system (DCS), it would not be possible to run the complex processes in such an optimal way. For a smooth flow of production it is essential that the batch record is structured consistently to ensure the manufacturing of products of constant form and stable quality.

The monitoring process in the active ingredient plant involves about 10,000 sensors and actuators distributed over 150 pieces of equipment, supplying essential data or carrying out instructions. With more than 1,000 processing operations executed in the Biberach plant, any action, i.e. every touch of a button, every temperature reading, and every transfer, is executed according to precise instructions and is subject to complete documentation. The MES system guides the operator safely and step by step through each work segment and prevents errors in operation. The importance of such a system for quality assurance can hardly be over-emphasized - being well aware of this, Boehringer Ingelheim started the BIOMES project as early as May 1999.

### 7.2.3 Manual and Automatic Sequences Alternating

The main challenge that the MES has to face is that in biotechnological production, automated workflows alternate with manual operations. For this reason, the automated sequences are first filed in the DCS recipe system and transferred to the MES. The MES then links these automated sub functions to the manual operations and consistency checks (e.g. batch or equipment status). Finally, target values are assigned to these manufacturing specifications.

The MES handles all the manual sequences and triggers the automated procedures in the DCS. On execution of automated sequences the DCS returns the result parameters to the MES. As the controlling system, the MES continually displays the current status of all processes including DCS. On completion of a manufacturing stage, the MES generates complete associated documentation.

The entire electronic process monitoring is designed to act as an early warning system. Trend calculations are used to detect and report deviations even before they actually occur, so that the operator has enough time to take corrective measures. On-line booking of every process step and every material consumption makes it possible to follow the process flow directly.

Another essential task of the MES is the monitoring of cleaning and sterilization status, including expiration dates for all related equipment, such as containers, pipe systems, and set-up parts. The risk of contamination is minimized, since the system would, for instance, issue an alarm as soon as an unsterilised pipe is to be used.

### 7.2.4 Suitable to Meet Future Requirements

Werum's PAS-X BIOTECH has made it possible for Boehringer Ingelheim to establish a central electronic production management system. This system can be interfaced to all relevant processes even outside the very area of production, such as laboratory information systems (LIMS). The MES serves as a data "turntable" and ensures consistent data flow between SAP and DCS environment.

## 8  Outlook

The cost-benefit ratio obtained by the implementation and operational use of an MES system always depends on the capabilities provided by the basic technologies. Today's new technologies show a trend towards open structures. In the field of basic software technologies J2EE is such an open standard. There is no longer the need to stick to one particular supplier. Further examples are XML and OPC interfaces, which facilitate a standardized data exchange. Currently, new technologies are launched at rapid pace enabling many other optimizations at low costs. Among these new trends are:

- Web-based functions: use of intranet/internet functions

- Mobile computing: use of mobile computers/handhelds

- PAT: analysis and intervention in realtime to avoid errors instead of analyzing them afterwards

- Modularization: use of J2EE, CORBA software architectures enabling an open system environment (best of breed) with standardized interfaces.

Many attempts to create an all-embracing overall system have failed so far and will probably also fail in the future. Some jobs have a rather universal character in all enterprises, such as the issuing and processing of invoices. Other tasks are very specific and restricted to particular production structures, such as the requirement to stage a given quantity of a material ensuring that all the material belongs to the same batch. With the prospect of steadily growing market potential, it will be one of the greatest challenges in the near future for IT and, thus, for MES applications, to develop the optimum structure for IT components associated with production processes.

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