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A Model for MES in Pharmaceutical Production -An AstraZeneca Case Study

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<i>Title and subtitle</i> A Model for MES in Pharmaceutical Production – An AstraZeneca Case Study. (En MES model för farmaceutisk tillverkning – Ett praktikfall vid EstraZeneca)			
<i>Abstract</i> <p>The objective with the master thesis project is to develop an <i>Electronic Batch Record</i> (EBR) solution for the AstraZeneca TPS division and map it to the ISA 95 model for <i>Manufacturing Execution Systems</i> (MES). The EBR solution in addition to current and new manufacturing systems will form an AstraZeneca TPS model for MES, which can be used for further evaluation and system development guidance.</p> <p>The first stage of the EBR development is to choose the most suitable <i>production area</i>, defined as a production line dedicated to a specific product group, for an EBR implementation. The selection is made according to product, technical, economical and risk criteria. Jointly they are estimated to give a valid indication of the suitability and potential benefits of introducing an EBR solution to a production area. When the most suitable production area is selected an extensive research of manufacturing procedures and systems is carried out. The identified systems together with project constraints and systems under development form a basis for the establishment of an AstraZeneca TPS EBR solution. Conceptual architecture for the EBR infrastructure is thereafter created and necessary EBR functionality is defined. The current systems and their functionality are mapped to the ISA 95 model for MES and presented together with the EBR solution to form an AstraZeneca TPS MES model. Subsequently, the benefits and detriments of the full EBR system are studied and discussed to additionally clarify the motives for introducing the system. Conclusively, certain metrics are introduced to measure the impact and the potential improvements gained from the EBR system implementation.</p>			
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1.0 INTRODUCTION

1.1 ASTRAZENECA BACKGROUND

AstraZeneca is one of the leading pharmaceutical companies in the world. The company employs over 64.000 people globally and 13.000 in Sweden. The corporate headquarter is located in London, UK, while the R&D headquarter is in Södertälje, Sweden. In Sweden AstraZeneca have R&D facilities in Lund, Mölndal and Södertälje whilst all the production is located to Södertälje. [7]

Sweden Operations is the link between R&D and marketing in Sweden. It is the largest manufacturing site within AstraZeneca and employs around 5.000 people. Activities within Sweden Operations comprise preparation of substances, formulation, and packaging. Tablets, liquid, turbuhaler, and bulk products are manufactured for a global market. Its production is primarily located in Södertälje while some packaging facilities are placed in Umeå. [7]

The pharmaceutical production in Södertälje is located on two separate manufacturing sites, Gärtuna and Snäckviken. The first site is more or less dedicated for tablet production whilst the latter produces liquid, turbuhaler and bulk pharmaceuticals. Traditionally these manufacturing sites belonged to different organisations, namely *Tablet Products Supply* (TPS) and *Liquid Products Supply* (LPS). However, a recent reorganisation joined the two divisions under the name *Drug Products Supply* (DPS).

1.1.1 Gärtuna Production Site

The Gärtuna production site is the worlds largest pharmaceutical tablet plant with 1.900 employees, producing more than 10 million tablets and capsules per annum. Tablets and capsules are produced in batches, meaning that a given quantity is manufactured as the result of one operation. In order to support the manufacturing process at Gärtuna a wide range of computerised systems are in place.

In 2001-2003 a major system for collecting manufacturing data was implemented in order to effectively cope with 21 CFR Part 11, which are regulations for *electronic records* ER and *electronic signatures* ES set by the *Food and Drug Administration* (FDA) in 1997. The centralised *Manufacturing Information System* (MIS) was introduced under the named *Process Information System Tablets* (PIST) and it collects data from more than 130 machines in the production area. Each machine is connected to PIST through a *Supervisory Control And Data Acquisition* (SCADA) terminal, which also allows operators to download recipes and access process evaluation tools. However, some equipment not being connected to PIST may have a stand-alone computerised system. Using PIST enables creation and analysis of production related *Key Performance Indicators* (KPI). Thus, the system simplifies the general improvement work, relying on *Six Sigma* principles, undertaken by AstraZeneca. Typically the benefits include easier identification of manufacturing bottlenecks, increased production efficiency and increased standardisation of work procedures. [14]

In pharmaceutical production, detailed manufacturing procedures are described by a paper based *batch protocol*, which is used by the operator. The batch protocol is also used for documenting manufacturing and is a central part of the batch documentation at the Gärtuna site.

1.1.2 Gärtuna Products

Sweden Operations supplies six of AstraZeneca's top ten most sold products. Four of these being produced at the Gärtuna site are described below. [8]

Atacand

Atacand is an angiotensin receptor blocker (ARB) used to reduce high blood pressure. The active ingredients for Atacand are candesartan, cilexetil and hydroklortiazid. [8]

Losec

The active ingredient in Losec is called omeprazole. Omeprazole is a proton pump inhibitor (PPI) that works by blocking a particular molecule in a type of cell in the stomach, so reducing the amount of stomach acid produced. The medicine is used to treat acid-related diseases. [8]

Nexium

Nexium is the successor to Losec and contains the active ingredient esomeprazole. Esomeprazole is a proton pump inhibitor (PPI) that works by blocking a particular molecule in a type of cell in the stomach, so reducing the amount of stomach acid produced. [8]

Seloken/Seloken ZOC

Metoprolol, the active ingredient in Seloken ZOC, is a substance known as a beta-blocker. A beta-blocker affects the heart in a way that reduces the heart frequency and blood pressure. The difference between Seloken and Seloken ZOC is the manner in which the tablet dissolves in the body. The three letters in ZOC stands for ZeroOrder kinetiCs, which means that the Metoprolol is emitted from the tablet at a slow and even speed. [8]

1.2 OBJECTIVES

The existing manual/computerised hybrid production system is not as efficient as possible. By introducing an *Electronic Batch Record* (EBR) and thus recording all production and process related data electronically, the entire production is believed to become more efficient, face fewer deviations and gain several other benefits discussed later in the report. The main objective with this master thesis is to develop an EBR solution and map it to the ISA 95 model for *Manufacturing Execution System* (MES). This will form a model for MES in pharmaceutical production, based on an AstraZeneca TPS case study.

1.3 PROBLEM DEFINITION

This master thesis primarily aims to develop an EBR solution at AstraZeneca TPS. The solution will be mapped on the ISA 95 MES model in order to define a MES for pharmaceutical production. It is of particular interest to evaluate the distinction between MES and EBR, which is generally weak. The problem to solve is defined as follows:

1. Select an appropriate manufacturing *production area* dedicated to a product group according to various criteria, defined in cooperation with AstraZeneca supervisors.
2. Suggest an EBR solution for the selected production area.
3. Define an AstraZeneca MES model based on the developed EBR solution.

1.4 CONSTRAINTS

Due to the potential scope of an EBR/MES project and the actual time frames, a number of constraints need to be set on the master thesis. The constraints are described in detail below.

Scheduling

At the Gärtuna site a Kanban system is used for detailed production scheduling. The deployment of Kanban a few years ago sincerely reduced lead-times and costs for *Work In Progress* (WIP). Even though Kanban is a success story at Gärtuna it is by many considered as an outdated scheduling method. It is assumed that utilising more sophisticated modern scheduling techniques can reduce costs for WIP and lead-times even further. However, production management explicitly wished that no further investigation of scheduling practices should be performed. Hence, scheduling functions are not considered in the master thesis project.

Manufacturing Systems

When constructing the EBR solution, only systems used by manufacturing operations are considered. Other systems such as management and accounting systems are disregarded. This also leads to the exclusion of systems used by inventory and packaging operations. The communication with these systems is however regarded and is handled through interfaces towards current systems. It is also desired to reuse current systems to the extent it is possible.

Lab Systems

In Process Control (IPC) procedures form an important part of manufacturing and product quality assurance. The IPC constitutes a significant part of the batch documentation and is often closely linked to advanced lab equipment. For controlling and managing these systems electronically, certain software, which is similar to common EBR software, is used. The lab systems are therefore not contained by the solution. If it is decided to develop the master thesis further, regards need to be taken to these systems since they form an integral part of the complete manufacturing and documentation process.

Implementation

The master thesis project provides a fundamental abstract design of an EBR system for a selected production area at the Gärtuna site. It is not aimed at providing any implementation of programme code or in detail defining communication procedures or protocols between personnel and systems.

1.5 METHODOLOGY

The master thesis methodology, displayed in Figure 1, was jointly developed with supervisors from the AstraZeneca TPP department and the Lund Institute of Technology. The project has two concurrent paths, a primary path with an EBR focus and a secondary path with a MES focus. The primary path concerns the development of an EBR solution while the secondary path involves a mapping of the current systems and the EBR solution to the ISA 95 model for MES. Since the secondary path is an application of the work performed in the primary path the latter constitute the main part of the thesis. Hence, the master thesis report follows the same structure as the primary path, which is shown in Figure 1.

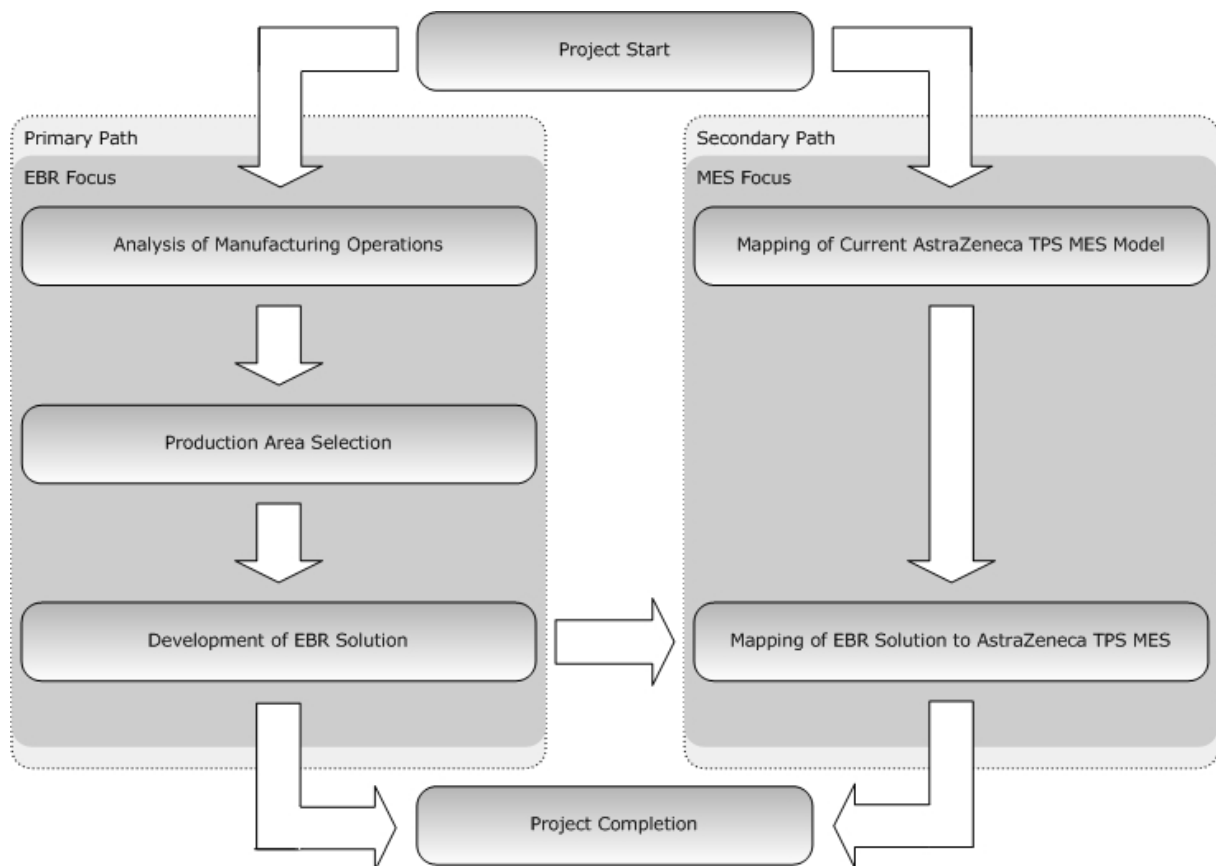


Figure 1: Methodology for the master thesis project

1.5.1 Analysis of Manufacturing Operations

Initially it is vital to gain knowledge of the general manufacturing process and its detailed procedures in order to identify problem areas and facilitate further satisfactory analysis. Hence, a fundamental mapping of the production operations at the Gärtuna site was undertaken. The mapping, which is enclosed in Appendix A, includes primary production equipment, secondary production equipment and cleaning equipment. The production flow mapping additionally covers production routing and MIS integration.

1.5.2 Production Area Selection

An initial objective with the master thesis project is to select the most appropriate production area dedicated to the production of a certain product group for the development of an EBR solution. To simplify this process a particular selection methodology was developed as displayed in Figure 2. Initially a number of production areas at the Gärtuna site, referred to as candidates, are selected. The feasibility screening discards candidates not suitable for an EBR solution regarding product and equipment related criteria. The remaining candidates are then evaluated regarding economic and sensitivity related criteria. A risk-return screening subsequently results in a ranking of the production areas.

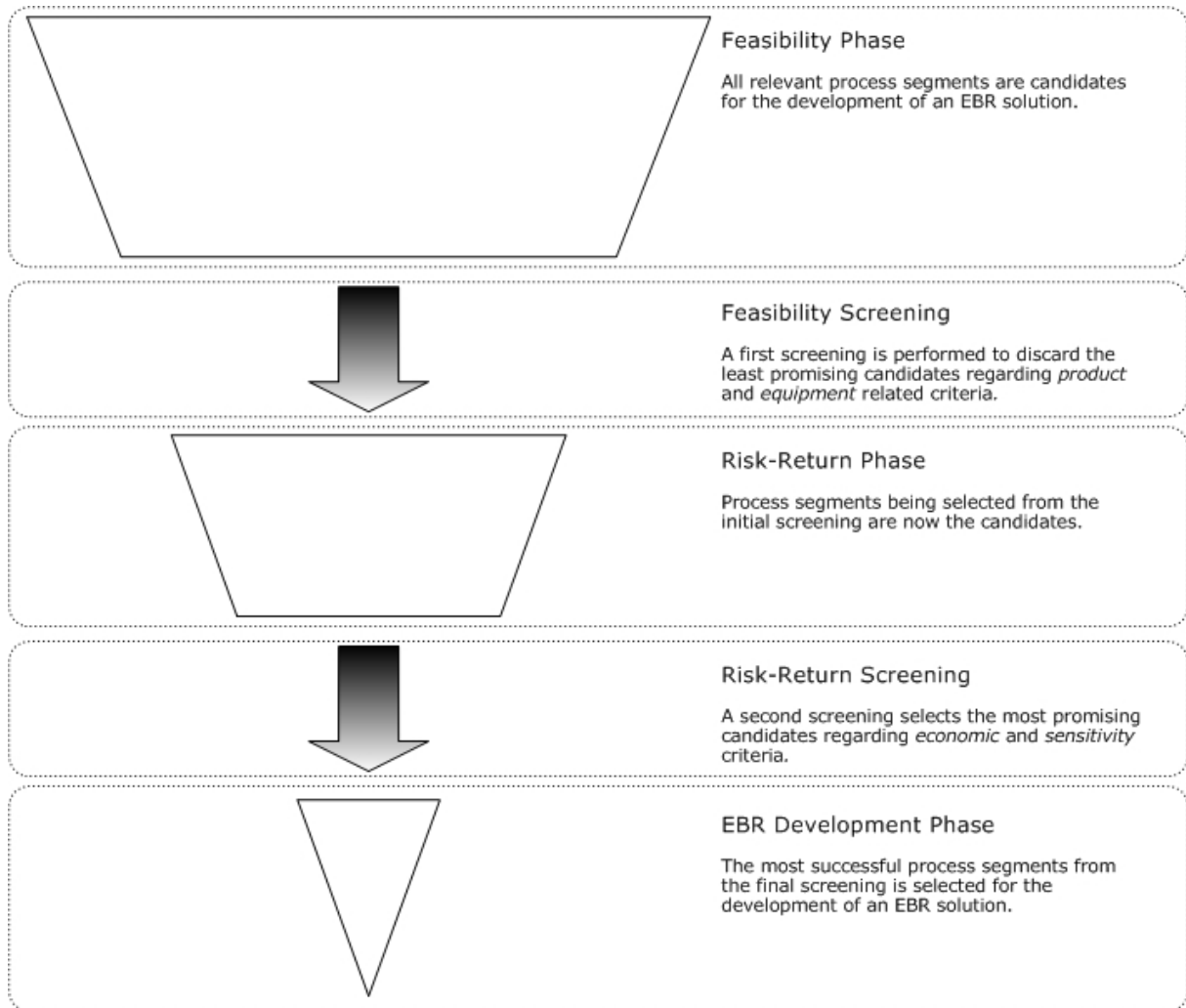


Figure 2: Methodology to select production area for the development of an EBR solution

1.5.3 Development of EBR Solution

The central part of the AstraZeneca TPS MES model is the EBR solution for the selected candidate. The process of developing an EBR solution is described in Figure 3. It is essential to identify necessary EBR activities at the selected production area and then relate them to the current systems. Some of the existing systems should form an integral part of the complete EBR solution, non-existing functionality will be included by new system introductions and most some of the current systems might be replaced, which need to be regarded. Interfaces between current and new systems should be established and general system architecture should be developed. The main purpose is not to provide AstraZeneca with a complete EBR solution but rather to provide material for a future EBR solution and demand specification.

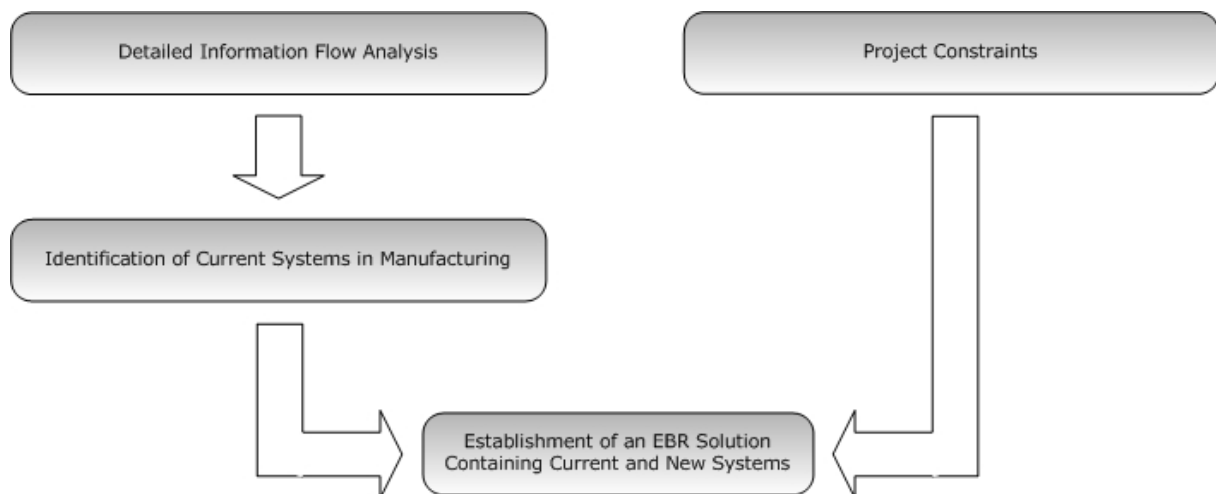


Figure 3: Process for EBR solution development

1.5.4 Mapping of Current AstraZeneca TPS MES Model

The current systems involved in the manufacturing process at the Gärtuna site are identified and mapped on the ISA 95 model for MES. ISA 95 provides a widely adopted model for MES and is supported by most EBR system suppliers. Hence, a mapping of the current Gärtuna systems to this model yields a suitable platform for the development of an EBR solution and in the establishment of interfaces between new and current systems.

1.5.5 Mapping of EBR Solution to AstraZeneca TPS MES

A mapping of the EBR solution to the AstraZeneca TPS MES model previously established gives a tool for showing the transformation of the current manufacturing system into having full EBR functionality. Such a mapping gives AstraZeneca TPS management an objective of which EBR functionality to focus on. It should further simplify the management of an EBR pilot project, improve the quality of an EBR business case and enable more qualitative discussions with EBR system suppliers.

2.0 THEORY

The theory chapter introduces and defines concepts, models and systems used and discussed during the rest of the master thesis. Further descriptions are given under the subtopics below.

2.1 DEFINITIONS

The definitions given in the subtopics are categorised by their relation to Gärtuna and manufacturing in general.

2.1.1 Manufacturing definitions

Batch

- 1) The material that is being produced or that has been produced by a single execution of a batch process. [3]
- 2) An entity that represents the production of a material at any point in the process. [3]

Batch Process

A process that leads to the production of finite quantities of material by subjecting quantities of input materials to an ordered set of processing activities over a finite period of time using one or more pieces of equipment. [3]

Batch Protocol

A batch protocol, also referred to as a *batch recipe*, is used when manufacturing a batch. The batch protocol is a step-by-step guide used by an operator to ensure the adoption of correct manufacturing procedures. The batch protocol contains blocks of manufacturing steps. The manufacturing steps can contain actions, quantities, routines and *In Process Control (IPC)*. After predetermined manufacturing steps, the operator needs to sign signatures to confirm that the actions, quantities, routines or IPC have been used and carried out as stated in the steps in the batch protocol. The operator also needs to document information in the batch protocol such as dates, quantities, time stamps etc. The batch protocol documentation is later used for manufacturing traceability reasons by the quality department. The protocol certifies product quality and can assist in deviation investigations.

Recipe

The necessary set of information that uniquely defines the production requirements of the product. [3]

EBR – Electronic Batch Record

EBR is a record and system managing all information central to batch production documentation. The information concerns manufacturing procedures, process data, quality control, resource specifications and production tracking.

ERP – Enterprise Resource Planning

Enterprise Resource Planning or Business Logistics system is the name for a set of activities that helps a manufacturer or other business to manage and integrate the important parts of its business. An ERP system integrates areas such as planning, purchasing, inventory, sales, marketing, finance and human resources. Typically it comprises product planning, parts purchasing, maintaining inventories, supplier interaction, order tracking and providing customer service. Generally, an ERP system uses or is integrated with a relational database system. [12]

IPC – In Process Control

Analysis made by an operator during the manufacturing process to assure product quality. The analysis include humidity tests, visual tests etc.

Kanban

Kanban, the Japanese word for 'sign', is one of the main tools in so-called *Just In Time* (JIT) systems. Such planning systems aim to optimise the material inventories at the manufacturing site. A Kanban system uses cards, carrying information about the parts (name, part number, quantity, source, destination, etc), or similar methods for materials replenishment. This is based a pull ordering system working in the following way. When a certain material volume is used from a stock (e.g. finished goods) the pull system triggers an order to refill the material or product with a predefined quantity. At Gärtuna the Kanban system uses Kanban cards containing article number and batch number. [2] [11]

MES – Manufacturing Execution System

A production scheduling and tracking system used to analyse and report resource availability and status, schedule and update orders, collect detailed execution data such as material usage, labour usage, process parameters, order and equipment status, and other critical information. It accesses bill of material, routing and other data from the base ERP system and is typically the system used for real-time shop floor reporting and monitoring that feeds activity data back to the base system. [9]

SOP – Standard Operating Procedure

A SOP or a routine is a step-by-step 'best current method' guideline aimed at reducing the variability of a procedural method. The SOP for example explains manufacturing procedures in further detail than the batch protocol. The batch protocol also often refers to SOPs when initiating procedures in manufacturing.

2.1.2 Gärtuna System Definitions

The Gärtuna site contains a considerable amount of in-house developed software that is specific for the site. AstraZeneca Sweden Operations had earlier no centrally governed IT strategy and different sites therefore developed own IT solutions. The lack of central IT strategy has given AstraZeneca high IT development and support costs. At this time there is however much work put in to developing a central joint IT strategy that will reduce site specific software over time and lower costs for IT solutions. The systems currently used at Gärtuna are described below.

GTS – Gärtuna Tillverknings System

GTS is the main component in recording and storing information concerning produced batches. GTS interacts with the production and scheduling management system *TPL* to exchange manufacturing data. TPL provides manufacturing orders to GTS that are used by the local planning department to schedule production. GTS returns manufacturing statistics to TPL, which is used to analyse production performance and to manage materials. GTS also communicates with the warehouse computer system *GFS* and is used to pre-order incoming materials for batches.

MSDM – Manufacturing Site Document Management

The MSDM database is used to store standard operating procedures, routines, batch protocols and other rules information. Guidelines and certain process values used for manufacturing products are in some cases only stored here.

PuP – Produktionsuppföljning Nyckeltal

The PuP system is used to analyse the utilisation of machines in manufacturing. The operators need to report to the PuP system e.g. when stops occur to explain the stop causes. The system contains many interesting statistics concerning utilisation, which can e.g. be used to optimise production.

QIMS – Quality Information Management System

QIMS is a computer software system used by the quality department as a tool for evaluating articles in manufacturing. The evaluation consists of stability analysis, lab tests and IPC results. The different evaluating data comes from different sources both in production and in the quality department. The system coordinates information from different inputs and generates an overall product assessment.

REF – Referensdatasystem

REF contains definitions of articles, materials, equipment and facilities. The system is often used to obtain article numbers and their descriptions.

SCADA – Supervisory Control and Data Acquisition

The SCADA unit is placed on site and is directly connected to a machine or a segment of the manufacturing process. The SCADA is used for manufacturing execution and the operator uses the unit to control and supervise the machine or process segment to which it is connected. Sensors mounted on process equipment in manufacturing, are connected to the SCADA. The values of the sensors are electronically recorded and paired with a timestamp; this is commonly known as a tag. After the tags have been recorded they are rerouted into the *PIST* system.

TPL – Tablett Produktion Ledning

TPL is the main tool for planning and managing the tablet production at Gärtuna. The program is complex and interacts with several other systems such as REF, TPR and GTS.

TPR – Tablett Processutveckling

The TPR system contains critical production definition data concerning article structure and manufacturing procedures. Other software such as REF and TPL uses the TPR information.

2.1.3 PIST

PIST – Process Information System Tablets

PIST is a *Manufacturing Information System* (MIS) that is developed specifically for Gärtuna. The PIST system is based on standard products from AspenTech and is primarily used for the electronic collection, storage and management of manufacturing and process data. The system consists of a number of different computer subsystems that have certain tasks and are responsible for different areas. The subsystems in PIST provide manufacturing recipe management, batch data, process data and audit trail. The system infrastructure is based on fibre optics, a set of different servers containing databases, SCADA units and so called scan nodes, which convert transmitted information between different communication protocols.

There exist two main database systems in the PIST system as shown in Figure 4.

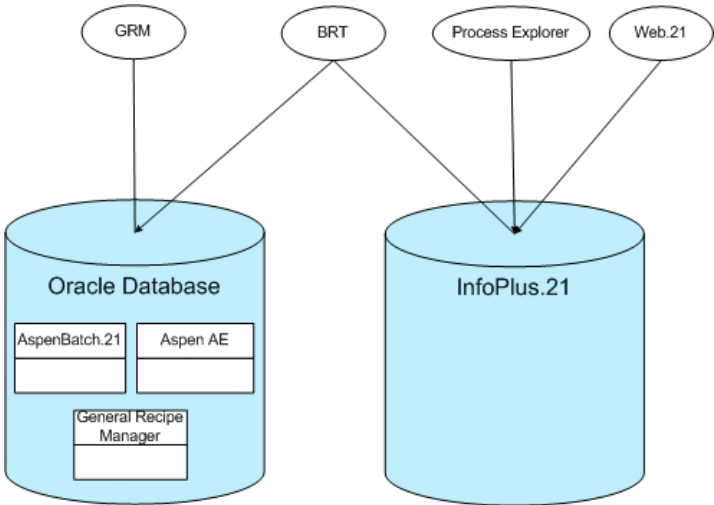


Figure 4: Current Oracle database system

InfoPlus.21

InfoPlus.21 (IP.21) is a Windows NT data server from AspenTech that constitutes a central part of the system. The database contains manufacturing process data being accessible for analysis and reports to users and other systems. All process data comes from sensors and are stored along with a timestamp. For using and analysing the process data a set of applications are used. The analysis applications consist of *Process Explorer* and *Web.21*. The applications can e.g. be used for trending and identifying *golden runs*. Other applications are also needed by the user to retrieve and present process data such as the *Batch Report Tool* (BRT).

Oracle

The current manufacturing system includes an Oracle database having several different schemas as displayed in Figure 4. *AspenBatch.21* (B.21) is one schema, containing batch specific data that form a natural part of an EBR such as article number, batch number and process start and stop times. Another schema is *Aspen AE* (AEE), which stores manufacturing alarms and events. The last major schema included in the database is the *General Recipe Manager* (GRM) being responsible for managing *manufacturing recipes*. Today there are a number of applications that retrieve or update information in these schemas such as the GRM application.

Manufacturing Recipe

A manufacturing recipe is defined as a set of process parameters that are used by the SCADA software as machine instructions when manufacturing a specific article.

GRM – General Recipe Manager

GRM is a vital part of the PIST system. GRM is an application on the Oracle database managing all manufacturing recipes for the machine equipment connected to the SCADA units. The system manages the download, edit, addition and deletion of manufacturing recipes. The recipes are downloaded by the SCADA software and thereafter put into the machine PLC.

BRT – Batch Report Tool

The Batch Report Tool is a client used to view and print batch reports. The application selects appropriate data from the Oracle and the InfoPlus.21¹ databases in the system. It is currently a vital part of the PIST system.

Batch Report

The batch report is an important part of the batch documentation. It contains selected process parameters taken from stored data tags. The last pages of a batch report usually contain graphs and trends of the measured tags over a period of time. The values, graphs and trends are later used for analysis by quality personal.

2.1.4 General definitions

ER – Electronic Record

An ER is any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system [15].

ES – Electronic Signature

ES is a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent to the individual's handwritten signature [15].

21 CFR² Part 11

21 CFR Part 11 is a set of rules and regulations, issued by the American Food and Drug Administration (FDA), which concern the creation and management of ER and ES [15].

¹ The InfoPlus.21 database system is described in subsection 7.1.7

² Code of Federal Regulations

2.2 ANSI/ISA 95

ANSI/ISA 95³ is a worldwide standard developed for the integration and generalisation of *Enterprise – Control* systems. An enterprise system⁴ defines and controls all business logistics and resource allocation activities of a company or an enterprise. The control system is rather defined as the physical operations and system architecture controlling the manufacturing process. Thus, it is executing the work being scheduled by the enterprise system.

2.2.1 Concept Description

Large and complex manufacturing systems are preferable separated into different levels or layers as displayed in Figure 5. It shows three layers called the enterprise layer, the manufacturing layer and the control layer. [4] [6]

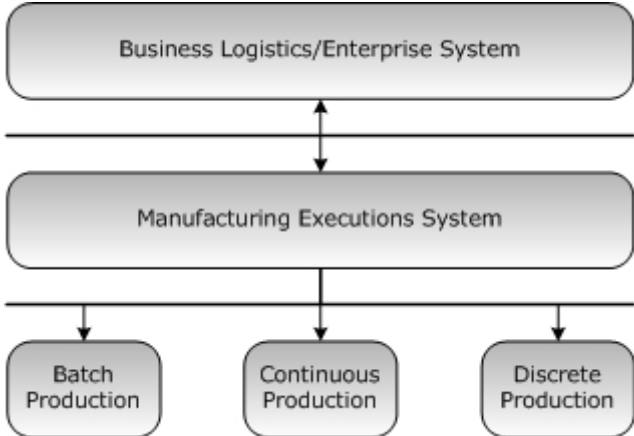


Figure 5: Functional hierarchy for enterprise-control systems

³ Usually referred to as ISA 95 or S95

⁴ Also referred to as an Enterprise Resource Planning System (ERP) or a Business Logistics System

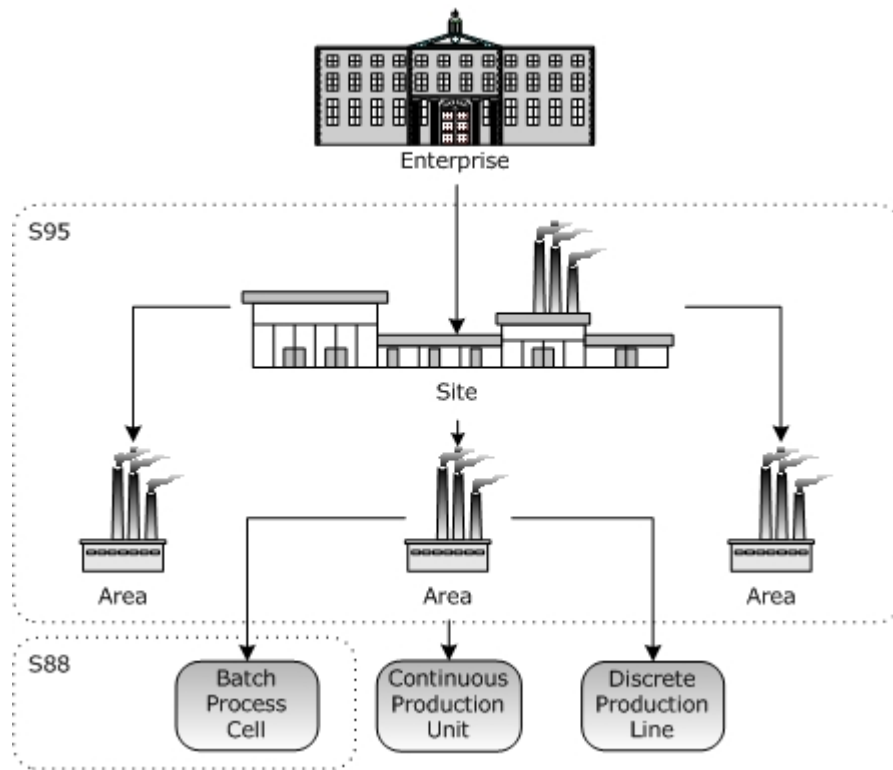


Figure 6: Equipment hierarchy for enterprise-control systems

The functional hierarchy, shown in Figure 5, describes activities and information flow in the manufacturing system whilst the equipment hierarchy, depicted in Figure 6, describes the physical order of *enterprise*, *site*, *area* and *batch process cells*⁵ involved in the enterprise-control system. The different levels in of the equipment hierarchy model in Figure 6 are defined in Table 1.

⁵ Continuous production units and discrete production lines are not used or discussed in the master thesis since they are not utilised in batch production.

Table 1: Definitions of the Equipment Hierarchy Level entities

Equipment Hierarchy Level	Definition
Enterprise	An enterprise is a collection of one or more sites and may contain sites and areas. The enterprise is responsible for determining what products will be manufactured, at which sites they will be manufactured and in general how they will be manufactured. [4]
Site	A site is a physical, geographical, or logical grouping determined by the enterprise. It may contain areas, production lines, process cells and production units. [4]
Area	A site is a physical, geographical, or logical grouping determined by the site. It may contain process cells, production units, and production lines. [4]
Process Cell	A logical grouping of equipment that includes the equipment required for production of one or more batches. It defines the span of logical control of one set of process equipment within an area. [3]

The ISA 95 standard describes how to develop a Manufacturing Execution System (MES) and its interfaces towards the enterprise and control system layers. A standard model for such systems modularises the solution in the sense that control and enterprise level systems are separated from each other and may interconnect systems from different manufacturers. Thus, it also allows changes in production processes without requiring unnecessary changes in the enterprise level systems. [6]

ISA 95 defines four types of information being communicated between the manufacturing and enterprise level, which are presented in Figure 7. The standard also defines *personnel*, *equipment*, *material* and *process segments* as the different resources being used in the manufacturing execution system. The ISA 95 model for MES, displayed in Figure 7, further describes which functions in the production system that communicates with the higher and lower level functions. It also describes essential functionality and typical information flow within a general production system. However, the model might need some customisation to industry and company specific aspects. ISA 95 defines four different views of the MES model. The *quality*, *inventory* and *maintenance* views have the same structure as the *production* view shown in Figure 8. However, project constraints make it superfluous to cover those views in the theory chapter. [4] [5]

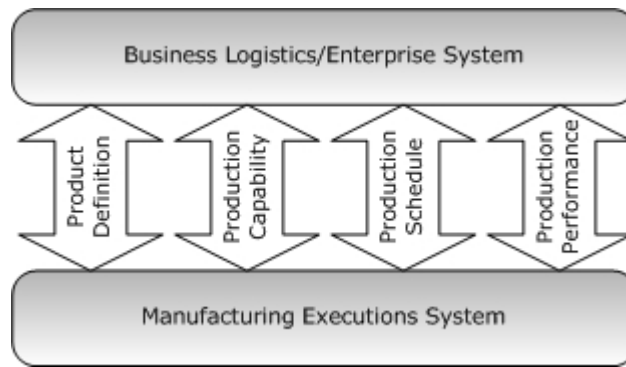


Figure 7: Information flow between enterprise level and manufacturing level

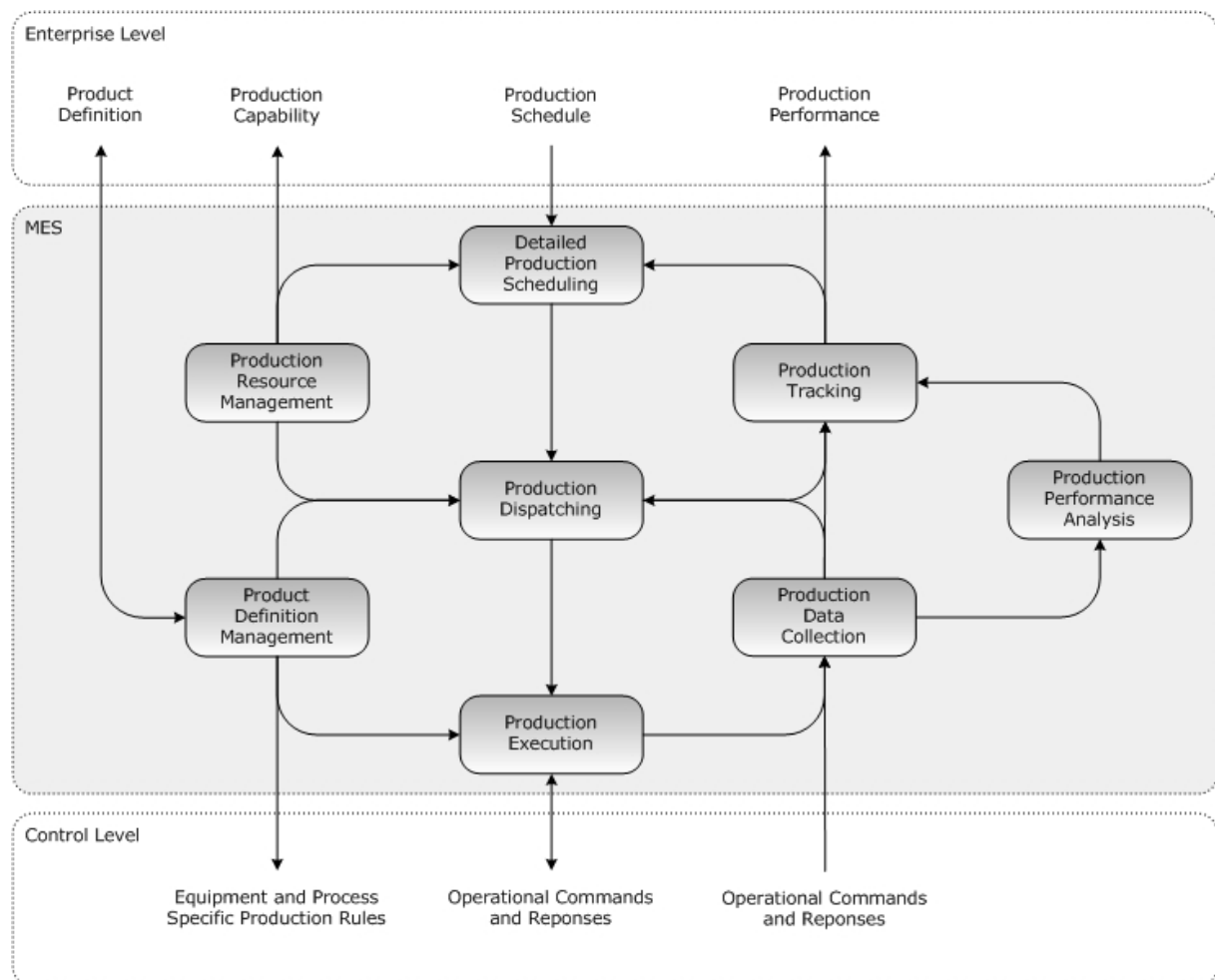


Figure 8: Production Operations and information flow defined by ISA 95

The activities in the ISA 95 MES model displayed in Figure 8 define different important production functionality described below.

Product Definition Management

The collection of activities that manage all the information about a product required for manufacturing. Product definition information is typically shared between product production rules, bill of material and bill of resources. [5]

Production Resource Management

The collection of activities that manage information concerning resources, such as material, equipment and personnel, required by production operations. Information concerning resource capability should be provided for scheduling activities and enterprise systems. [5]

Detailed Production Scheduling

The collection of activities that determine the optimal use of local resources to meet the production schedule requirements. This could involve ordering requests for minimal equipment setup or cleaning, merging or splitting requests when required due to batch sizes or limited production rates. [5]

Production Dispatching

The collection of activities that manage the flow of production by dispatching production to equipment and personnel. This could include maintaining the status of work orders (e.g. approved, fixed, in process or cancelled) and ensuring that process constraints are met in production. [5]

Production Execution Management

The collection of activities that direct the performance of work as specified by the production dispatch list and initiate control level activities. This further involves ensuring that correct and valid resources are used in production and confirming that the work is performed according to accepted quality standards. [5]

Production Data Collection

The collection of activities that gather, compile and manage production data for specific work processes or specific production requests. The collection concerns any kind of data, such as sensor readings, equipment states, event data, operator entered data, transaction data, operator actions, calculation results etc. [5]

Production Tracking

The collection of activities that summarise and report information about personnel and equipment used in production, material consumed, material produced, production costs and performance analysis results to enterprise systems. Additionally, it provides similar information to the detailed production scheduling activity. [5]

Production Performance Analysis

The collection of activities that analyse and report production performance and costs to business systems. This includes analysis of information of unit cycle times, resource utilisation, equipment utilisation, equipment performance, procedure efficiencies and production variability. Additionally, these analyses underpin KPI reports as well as the establishment of *golden runs*⁶. [5]

⁶ A golden run is the best run ever made

2.2.2 Equipment Hierarchy Mapping

The ISA 95 equipment hierarchy model can be mapped on to AstraZeneca Sweden Operations. The current ISA 95 equipment hierarchy mapping used at AstraZeneca Sweden Operations is summarised in Table 2. An example of the mapping of the equipment hierarchy model to AstraZeneca Sweden Operations is further visualised in Figure 9.

Table 2: Equipment Hierarchy mapping

Equipment Hierarchy Level	AstraZeneca Example
Enterprise	AstraZeneca Sweden Operations
Site	AstraZeneca Gärtuna site
Area	A production line dedicated to a product group
Process Cell	A well defined production element of an area

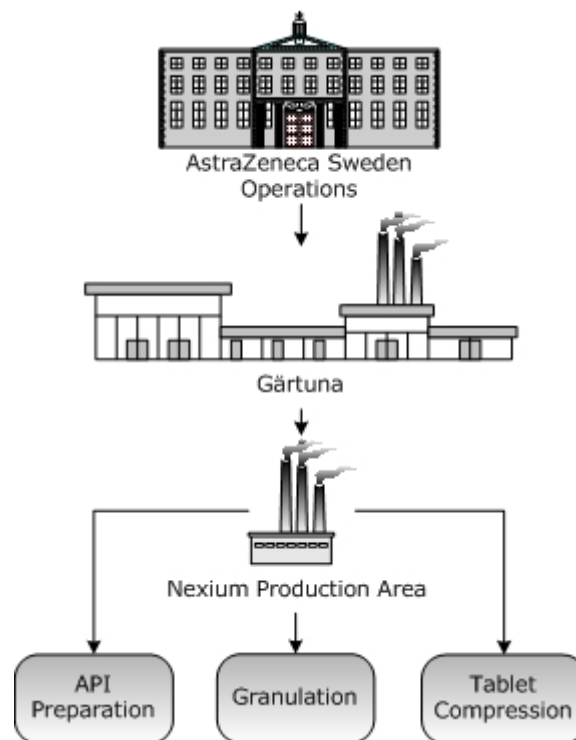


Figure 9: An example of the equipment hierarchy at AstraZeneca Sweden Operations

2.3 ELECTRONIC BATCH RECORD

An *Electronic Batch Record* (EBR) system facilitates paperless batch production. It should contain necessary information to enable traceability of the final product regarding equipment, facilities, materials, personnel, work practices and master formulas. The definition of an EBR is somewhat subjective and it contains many of the activities usually included in the ISA 95 MES model. An EBR is therefore commonly mistaken for a MES. This is clearly confusing and not advantageous for the business in general. However, major EBR system providers typically define the included functionality according to Table 3. [13] [14]

An EBR system should generally contain most of the MES functionality except for scheduling and performance analysis. These functionality are indeed vital for optimal process performance but are rather related to production performance and quality than batch documentation. Our definition of an EBR system is shown in Figure 10. The yellow shaded background highlights the EBR activities. A remark is that production dispatching is partly regarded as an EBR specific functionality. This is due to the workflow management functionality, including rules enforcement and deviation management in Table 3, which handles some but not all of the production dispatching tasks. It is sometimes argued that an EBR system may exist without such functionality but that way the system would be far less beneficial to implement. For instance, real-time deviation management allows for fewer deviations, scrap decrement potential and lower lead times in the quality control operations.

Table 3: Definition of EBR functionality

Functionality	Description
Paperless Production	The entire production process should be paperless and comply with 21 CFR Part 11. Physical batch protocols, production and deviation reports should be managed in a paperless manner.
Procedural Guidance	The operator should be informed in detail how to produce a batch. For instance SOPs and routines should be accessible as well as specific manufacturing details regarding process limits. Most EBR systems provide intelligence in terms of procedural guidance for the operator for each step in the manufacturing process.
Rules Enforcement	Rules enforcement ensures that production rules are adopted and the operator is generally not allowed to proceed to the next step if the manufacturing rules are not fulfilled. The rules enforcement functionality also ensures that the batch is documented correctly and fully.
Deviation Management	The EBR system continuously compares real-time process values to required and target values. If a deviation occurs the operator should be informed. If the deviation affects the final product the operator should not be able to proceed to the next step in the manufacturing process until it is corrected. However, the operator may disregard some low priority deviations but such actions should always be traceable in the batch reports for quality analysis purpose. For instance, if manual weightings do not agree with target values the operator must correct this operation before advancing to the next step.
Control of Material Flow	Received materials identity and quantity should be verified before entering the manufacturing system. This minimises the risk of using wrong materials in the manufacturing process.
Audit Trail	Production process values, alarms, events and other data should be stored in a database system in order to allow for real-time and historical analysis. All changes to process values occurring during manufacturing should be recorded in a database complying with the 21 CFR Part 11 regulations.
Electronic Logbook	All machines and manufacturing equipment needs a GMP compliant logbook for traceability and status reasons. A GMP compliant logbook typically keeps information about previous production runs and cleaning statuses. Such functionality is obviously also important to include in an EBR system.

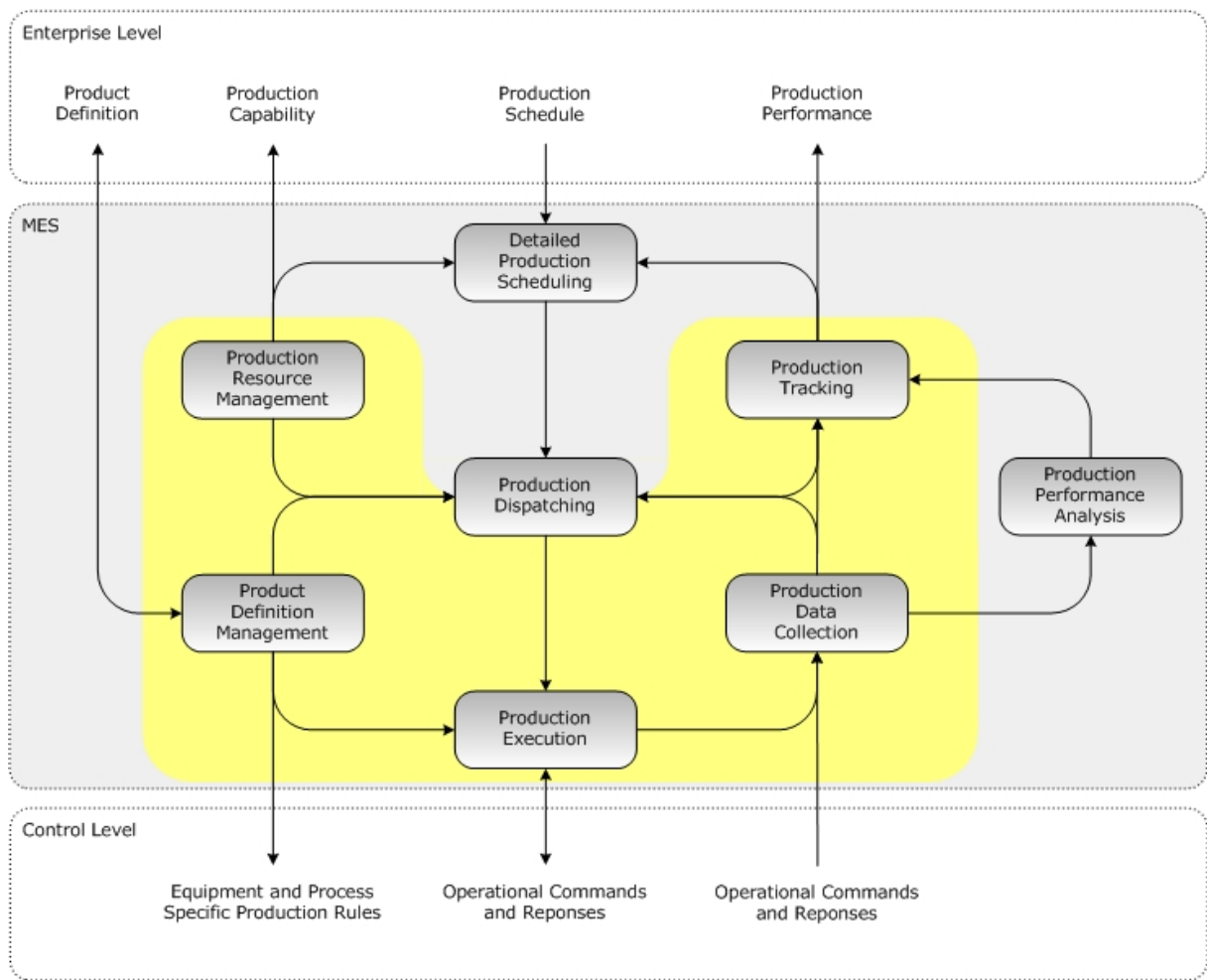


Figure 10: Definition of EBR in yellow shading mapped on the ISA 95 model for MES

3.0 ANALYSIS OF MANUFACTURING OPERATIONS

To gain a thorough understanding of the AstraZeneca TPS manufacturing system it was important to perform a detailed production process analysis. A considerable emphasis was put on this task at the initial stages of the project. At first a general analysis of the production was performed, which then was followed by a production workflow analysis of the entire site.

3.1 GENERAL MANUFACTURING PROCESS

To simplify the understanding of tablet manufacturing and production flow at Gärtuna, a few manufacturing definitions and process descriptions are given and explained below. The general manufacturing process for tablets and capsules are shown in Figure 11 and Figure 12 respectively.

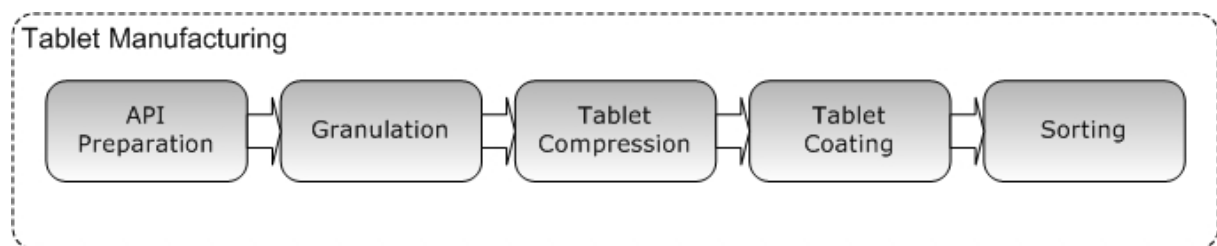


Figure 11: Main steps in the tablet manufacturing process at Gärtuna

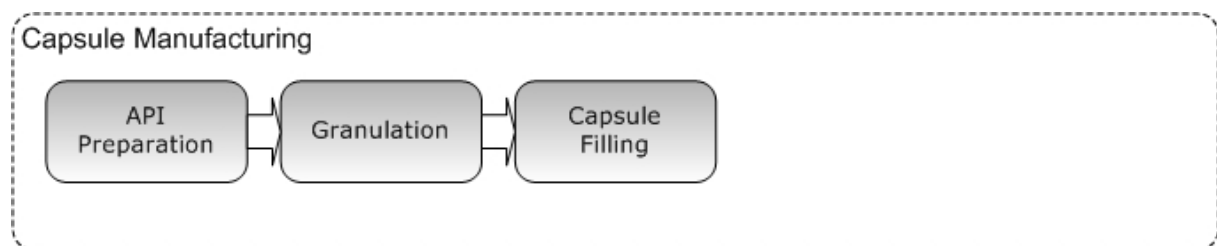


Figure 12: Main steps in the capsule manufacturing process at the Gärtuna site

3.1.1 API Preparation

The *Active Pharmaceutical Ingredient* (API) is any substance or mixture of substances that is the active ingredient of the product. In other words, API is the substance that furnishes pharmacological activity to the body. [10]

At AstraZeneca TPS the raw material is delivered from the storage and dispensing areas. Commonly, some of these are blended into an active substance mixture to be used in the next stage of the manufacturing process. The substance can be described as fluent and dense.

3.1.2 Granulation

The granulation process involves a number of process steps to produce tablet or capsule granules. Based on a spherical core, a number of layers with certain properties are added in order to give the granule its unique properties. The number of layers and its functionality may differ depending on the product group or type, e.g. whether a tablet or capsule is produced. However, the different layers typically include API, *Control-Release* (CR) properties that manage the dissolution of the active ingredient in the human body and a protective layer. The coating film is sprayed on using a *Fluid Bed Dryer* (FBD).

3.1.3 Tablet Compression

The first step in the tablet compression process is to mix the received tablet granules into a homogenous mixture of particles along with other ingredients such as cellulose. The mixing is usually done in a nauta mixer, which is commonly dedicated to a certain tablet compression machine. The nauta mixture provides the tablet compression machine with granules that are compressed into tablets. The mixture is fed into a matrix inside the tablet compression machine. It is thereafter compressed to tablets between two punches using high pressure.

3.1.4 Tablet Coating

When the tablet compression is completed, the tablets need additional processing before the customer can use them. A coating solution is therefore added to the tablet. The coating is done in a large barrel, resembling a tumbler dryer, where the coating solution is sprayed on to a spinning bed of tablets. The coating solution serves an important functionality since it adds additional features, such as flavour, colour, lubrication and protection to the tablet.

3.1.5 Sorting

Finally, the compressed and coated tablets are sorted to filter out damaged tablets. This is partly done by visual inspections from operators but also through weight controls and through tablet shaking equipment.

3.1.6 Capsule Filling

The first step in the capsule filling process is to mix the received capsule granules into a homogenous mixture of particles. This procedure is often done using a tumbler mixer that is separated from the capsule filling machines. The homogeneous mix is then fed into the capsule fillers, which fills one part of the cap with granules. The other half is attached to the filled cap closing the capsule and completing production.

3.2 PRODUCTION WORKFLOW ANALYSIS

Gärtuna is a very large and complex production site. Much of the equipment is different and the manufacturing processes are considered as multifaceted. Hence, at an initial stage it was necessary to perform a production workflow analysis to gain a general understanding of the equipment and the different workflows existing in the manufacturing operations.

A study of the workflow mappings found in Appendix A reveals that there are great differences in the complexity of the workflow between production areas at AstraZeneca TPS. From the mappings it is clear that some production areas have a particularly large number of manufacturing steps that should make them more complicated to fully integrate with an EBR solution. However, due to great variations in the scope of work and the equipment used at different production steps such conclusions are difficult to make by just studying the maps in Appendix A. However, a feasible and relevant analysis is to compare the degree of PIST integration between different production areas. Additionally, it is possible to get an indication of the modernisation of a production area by comparing SCADA operating systems in different production areas. Areas having few SCADAs indicate a low degree of modernisation while production areas possessing many SCADAs with new operating systems imply a high degree of modernisation.

4.0 PRODUCTION AREA SELECTION

The objective with the production area selection is to identify the most suitable production area for the implementation of an EBR system. The candidates in the selection process are production areas dedicated to the production of a certain product group. The candidates are evaluated regarding a large number of criteria and finally the most suitable candidate is selected for the development of an EBR system.

The criteria used in the selection process are thoroughly defined and described in section 4.1. To enable an evaluation of the candidates regarding these criteria, a number of minor projects were carried out to extract fundamental candidate information. These projects followed the selection process methodology described in subsection 1.5.3 and are further discussed in section 4.2.

The actual selection process is covered in section 4.3. It also follows the methodology established in subsection 1.5.3 and is focused on criteria analysis and candidate evaluation.

4.1 CRITERIA

To enable the evaluation of candidates, a number of selection criteria need to be defined. The selection criteria are divided into four different types: *product criteria*, *equipment criteria*, *economic criteria* and *risk criteria*. The selection process is performed by two screenings focusing on *feasibility* and *risk-return*.

The feasibility screening is based on the product and equipment criteria types, describing the manufacturing systems from a product-related and technical perspective. It covers important criteria, which need to be satisfied in order to enable a successful EBR implementation.

The risk-return screening covers economic and risk-related criteria types. The outcome of the risk-return analysis is the most beneficial candidate, from a financial perspective, for an EBR implementation. The primary focus is on economic criteria but risk aspects are also imperative to consider, particularly when developing an implementation strategy since a proactive work in the concerned areas could lower the project risk. However, risk criteria are regarded as secondary to the economic criteria type in the selection process.

Quantitative criteria are strongly desired when evaluating candidates against each other. It enables a transparent assessment that minimises the involvement of personal judgements. Thus, each criteria type is broken down into a few criteria groups, which are further divided into some criteria. This way, each criterion is focused on one or a few particular metrics that in most cases are measurable.

4.1.1 Product Criteria

The candidates are evaluated regarding criteria such as production volume, production volume trend and article spread. The analysis indicates a candidate's current and future importance for the production site and its suitability to an EBR implementation.

4.1.1.1 Product importance and suitability

Production volume

Production volume and product profit margin are perhaps the most important drivers to product profitability and importance to the firm. Due to confidentiality reasons product profit margins are not studied in the master thesis project. However, the cost reduction potential with an EBR project is studied. Given a constant sales price a reduction in the manufacturing costs drives the margin up and hence, makes the product more profitable. A candidate showing high production volumes and a great potential reduction of manufacturing costs with an EBR system introduction is therefore regarded as being a potentially promising candidate. The cost savings per batch involve many different factors such as labour reduction, lead-time reduction and deviation decrement, which can differ between production areas. These factors are covered in subsection 4.1.3.

A remark is that high production volumes generally not only lead to higher manufacturing frequencies but also to slightly larger batch quantities. The increase in batch size often increases the batch documentation and quality related workload, which also increases the effects on the cost saving magnitude of an EBR system. The total cost savings are therefore regarded as being proportional to the production volume. Hence, concerning production volume an EBR system would have the greatest cost saving magnitude on a high volume production area.

Production volume trend

Analysing production volume trends is a simple but powerful prognosis-instrument for evaluating product demand from customers. A strategically important product group typically displays consistent or increasing sales volumes with respect to other products. In reality some products may be of high strategic importance even though not being particularly profitable. However, it is desirable for each product to cover its own expenses and therefore non-profitable goodwill products are disregarded. Given this simplification, volume trend evaluation is a useful quantitative measure of a product group's and a production area's strategic importance and future production volumes. A candidate with a high strategic importance and future production volume is regarded as suitable for an EBR implementation.

Article spread

When comparing separate production areas, which in many cases are dedicated to certain product groups, it is important to evaluate their article spread. A great article spread would significantly complicate an implementation of an EBR solution. The configuration process would have to be carried out for each article, which would be time-consuming and immensely expensive. Not configuring an EBR solution to all articles in a manufacturing facility is not particularly desirable since most facilities do not possess dedicated organisational structures for single articles. The organisation would have to deal with higher complexity due to hybrid batch documentation. In such manufacturing facilities a full EBR implementation is likely to be very expensive and erroneous in an initial stage.

4.1.2 Equipment Criteria

Each candidate is analysed regarding different equipment criteria, such as technical suitability and scalability. The equipment criteria primarily concern MIS integration, equipment standard and scalability potential, which are critical success factors for an EBR system implementation. For instance, high system upgrade and scalability costs are associated with selecting a production area having low equipment criteria suitability.

4.1.2.1 Technical suitability

MIS integration

An EBR solution must evidently be compatible with existing systems and infrastructures. At the Gärtuna site there have already been extensive investments in manufacturing systems, where PIST is a recent example. Typically, MIS systems constitute an integral part of a complete EBR solution by enabling important features such as production data collection, production tracking. When integrating the EBR solution with existing systems, significant costs can be reduced and initial operational problems prevented by choosing a production area that is already connected to the MIS system. Thus, it is important to evaluate the MIS integration between manufacturing equipment to determine the most suitable location for an implementation.

Equipment standard

Equipment age and diversity can have a great impact on a production area's technical suitability for an EBR implementation. An old and diverse equipment park is obviously not preferable to a modern and less diverse machine park. The latter should involve less configuration, integration and customisation of the EBR solution than the former alternative.

4.1.2.2 Scalability

Standardisation

It is favourable to select a production area that displays great internal and external standardisation. Internal standardisation facilitates implementation and configuration advantages within an area while external standardisation comprises scalability potential to other production areas. Choosing a process segment with high scalability potential can reduce configuration, integration and customisation work. When selecting the most promising candidate for the implementation of an EBR solution, the internal standardisation is more important than the external due to its direct affect on project costs. External standardisation primarily concerns a complete site implementation.

4.1.3 Economic Criteria

A central part of the selection process is to evaluate the candidates' potential to gain economic benefits from an EBR solution. The economic criteria group includes the most relevant criteria that have direct influence on cost savings. However, an EBR system would also have indirect effects on the production area profitability. It would be very difficult to quantify the cost reductions related to indirect factors such as improved product quality and working environment and therefore these are covered in the project.

4.1.3.1 Scrap decrement

EBR-related Scrap

An EBR system influences the scrap value in two significant ways that are deviation dependent. The first way is through a reduced number of deviations, which in turn will reduce the number of scraps per annum.

The other significant way is by making the deviation investigations more effective. This will shorten lead-times and reduce the amount of products being out-dated and thereafter scrapped. The greater scrap value the candidate has the more likely it is to reduce this by an EBR implementation. Hence, candidates with large scrap values are regarded as potentially successful with an EBR system.

4.1.3.2 Deviation decrement

An EBR system should increase procedural compliance while decreasing deviations related to documentation and production. Deviation decrement and procedural compliance can reduce significant amounts of costs. In some cases there may be substantial differences in cost savings between production areas due to manufacturing circumstances and production volumes. In order to fully capture the cost saving potential it is imperative to investigate the deviation decrement potential as a proportion of total deviations combined with the total number of deviations. This is usually highly correlated with production volume. Since production volume is analysed in the feasibility screening only deviation decrement potential of total deviations is analysed in this part of the risk-return screening.

4.1.3.3 WIPV decrement

A decrement of *Work In Progress Value* (WIPV) yields excess capital and reduced costs that, for instance, could be invested in securities to increase net income. When discussing a decrement of WIPV a couple of different KPI factors are of particular importance. These are described in Table 4 and the relation is shown in the formula below. [1]

Table 4: WIPV factors and their definition

Factor	Description
<i>WIP</i>	The amount of products in production
<i>WIPV</i>	The value of WIP
<i>p_a</i>	The average value of a product in production
<i>D</i>	The production demand per time period
<i>LT</i>	The lead-time for a product in production

$$WIPV = p_a \times WIP = p_a \times D \times LT$$

Lead-time

One of the main benefits from an EBR system implementation is a potential reduction of lead-times. Lead-times can be considerable, largely due to quality control related processes. Although, planning and scheduling also have major impact on the lead-times this is not investigated further in the master thesis project. If a candidate has high lead-times, it is regarded as having high potential of reducing WIPV and is therefore a beneficial candidate.

Value of Production Volume

Calculating the value of production volume according to the formula below enables a comparison of the magnitude of the production area's potential WIPV decrement. A high value of production volume will reduce WIPV more than a low value of production volume if lead-times are shortened. [1]

$$\text{Value of production volume} = p_a \times D$$

4.1.3.4 Labour decrement

An EBR system facilitates a high degree of automation, which has great potential of reducing labour in many instances of production and quality control. This yields great opportunities for a more efficient production and, thus, cost savings. The system also facilitates a shift from a reactive to a proactive work culture. In fact, a substantial labour reduction could be partly offset by an increase in proactive work, such as trending and maintenance. Although, this could result in improved product quality and indirect cost savings it is out of the scope for the master thesis project to further investigate.

The labour reduction can be divided into two categories, operative labour reduction and quality control labour reduction.

Operative Labour

The reduction of operative labour includes tasks handled by an operator that can be removed or simplified with an EBR system, e.g. logging, calculating and measuring documentation data. An EBR system will cause considerable reconstructions of the batch protocol, which most likely will lead to easier and more standardised work procedures.

Quality Control Labour

The most substantial labour reductions yielded by an EBR system should be in quality control operations. Most of the work with validating batch protocols for manual errors will become superfluous and the rest of the revision and evaluation process will be simpler and less time and labour consuming.

4.1.4 Risk Criteria

Sensitivity analysis is of importance when selecting a production area for the implementation of an EBR system. A sensitive area is particularly receptive to production disruptions and product deviations. Thus, it could be affected in a negative way by the implementation of new systems and is therefore regarded as being a less suitable selection than a robust area.

4.1.4.1 Sensitivity to disturbance

There are many factors influencing a production area's sensitivity to disturbance. Work procedures, equipment utilization and product value are typical factors that influence a system's sensitivity to disturbance and also suitability for modifications. The sensitivity is closely related to the risk of losing capital in the event of expected/unexpected production disturbance. Product groups can also have high strategic importance and complex production processes, which make their production areas sensitive to disturbance. However, these aspects are out of the project scope and are not investigated further. A number of measurable sensitivity criteria were established for the selection process, these are discussed below.

Utilization

Utilization gives valuable information about spare capacity and workload. A production area with high equipment utilization is considered to be more sensitive to disturbance than an area with low utilization.

Bottlenecks

Another important factor to consider is bottlenecks in production. This is a criterion, which is more specific than utilization in general. A manufacturing area with bottlenecks is more vulnerable to production disturbance than one without significant bottlenecks. Hence, there is an increased risk of delaying products and losing capital with the occurrence of bottlenecks in the production.

Cost of Goods Manufactured⁷

The cost of manufacturing a product largely decides the magnitude of lost capital in case of production disturbance. A product with high manufacturing costs, primarily due to high costs of raw material, is generally very sensitive to production disturbance.

⁷ Cost of goods manufactured is commonly referred to as CoGm.

Deviations per Batch

Deviations per batch is an important metric to study when analysing production area sensitivity to disturbance. It is calculated by dividing the total number of deviations with the total amount of batches produced. The metric indicates which production areas or process cells are less robust than others.

An implementation of an EBR system could initially increase deviations in a production area. In such a case a vulnerable production area is regarded to suffer more than a robust production area. An EBR implementation could in this area convey undesired complex problems that might potentially yield high costs. However, most of these problems tend to disappear with the evolvement of the system [13]. A high deviations per batch percentage could to the contrary also argue that the production area is particularly receptive to deviation decrements in the long run but this overlooked in the project

4.2 RESEARCH

To investigate the chosen selection criteria for the candidates, a number of different analytical tasks were carried out. The tasks sometimes coincide with one and another and fragments can be used under different criteria topics. The analytical tasks performed during the feasibility phase were made for all initial candidates. Additional criteria research had to be performed for the candidates in order to enable a risk-return screening. This criteria research is presented under the topic risk-return phase.

Due to a great strategic importance for AstraZeneca most of the values established in the criteria research section has been classified as confidential. Consequently, the criteria analysis in subsection 4.3 is presented as a comparison of candidates without displaying any established criteria values.

4.2.1 Feasibility Phase

During the feasibility phase, work was conducted to acquire material as a foundation for evaluating the suitability of the candidates regarding feasibility criteria. The primary material research is discussed in the subsections below.

4.2.1.1 Product importance and suitability

Production Volume

Production volumes are primarily evaluated regarding the number of units⁸ produced but also concerning the number of batches. The volume data is on a monthly basis and was received from the TPP department and thereafter transformed into a suitable format. Figure 1 shows the production volumes for the candidate production areas evaluated in the selection process.

⁸ A unit is equivalent to either one tablet or one capsule.

For confidentiality reasons the actual volumes cannot be presented in this report. However, the relative production volume between the candidates is clear from the diagram. A study of the diagram indicates that there could be a season effect in the time series, which is important to consider when analysing the production volumes.

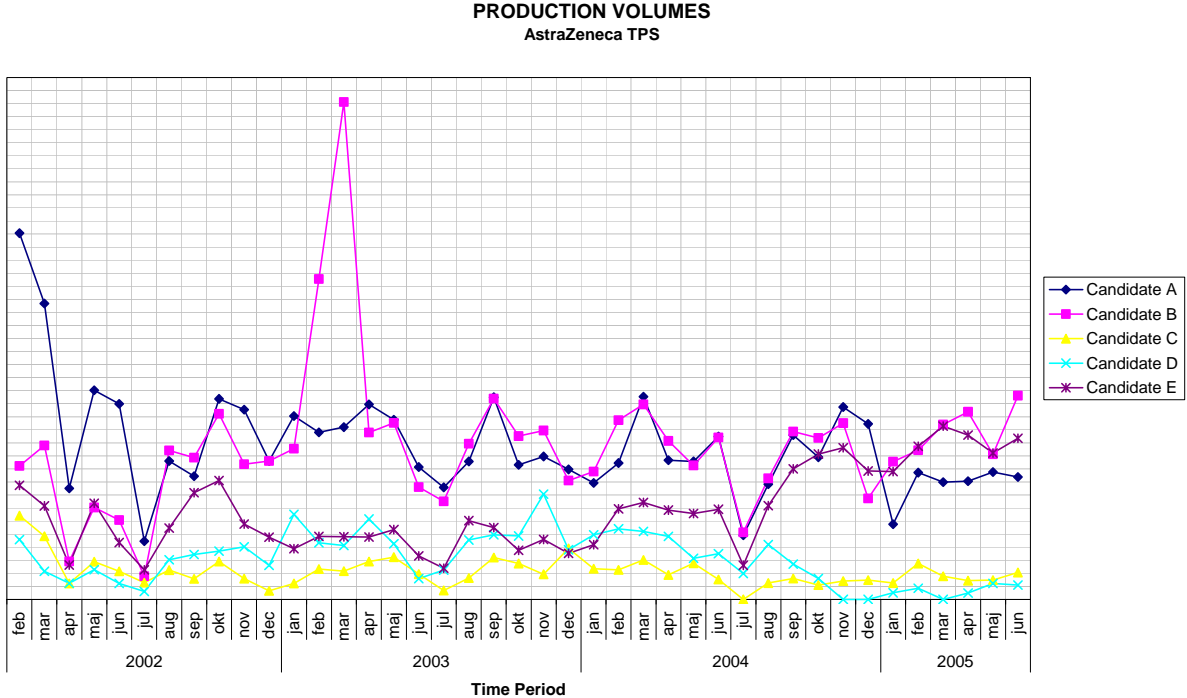


Figure 13: Relative production volume for investigated candidates at the Gärtuna site

Production Volume Trend

The production volumes were trended using linear regression models in order to get an estimate of the future production volumes and, thus, strategic importance. The forecast method is rather simple but gives valid indications of the volume trends.

Article Spread

The production volumes are deceptive to compare between production areas if the article spread is not taken into count. Consequently, all batches produced during the first half of 2005 where evaluated with data received from the GTS. The batches were ordered and summarised after ascending article number and the article spread was thereafter calculated.

4.2.1.2 Technical suitability

MIS Mapping

In order to evaluate the MIS integration of the production areas it was necessary to map existing manufacturing equipment connected to PIST. The mapping was based on existing documents received from the TPP department in combination with studies of production facilities and informal interviews. Finally, the PIST mapping was added to the workflow maps in order to give a comprehensive picture of equipment integration and execution flow. These maps are found in Appendix A.

4.2.1.3 Equipment standard

Equipment mapping

An equipment map was created to enable a comprehensive and accurate equipment comparison regarding type and standard. For each candidate production area, the manufacturing equipment was mapped concerning manufacturer, model and type. Regards were also taken to rebuilds and equipment customisation.

4.2.2 Risk-Return Phase

Those candidates passing the feasibility screening are further investigated and analysed in the risk-return phase. To retrieve candidate information regarding the risk-return criteria, a new set of analytical research tasks were undertaken. The tasks are presented under the topics below.

4.2.2.1 Scrap decrement

The link between EBR and reduced scrap costs was important to investigate further. In order to establish the relationship it was essential to analyse the underlying reasons for scrap cost occurrence. The scrap cost causes can be classified as EBR-related, uncertain or non EBR-related depending on their probability of being reduced by an EBR system. Large efforts were put in to obtain the underlying information but without success. However, informal interviews with personnel established that a substantial but unspecified amount of the scrap costs could be reduced with an EBR system.

4.2.2.2 Deviation decrement

To retrieve the deviation decrement potential, the link between EBR and deviation causes needed to be established. The TQ⁹ department keeps records of deviation statistics that contains descriptions of the factors causing the deviations. The deviation data in the research task was kept in separate documents and had slightly different formats depending on which organisation within the TQ department that were mastering them. Hence, the documents were adjusted for compatible reasons before they were merged into one spreadsheet. After the merge, the deviations were classified into three different categories, depending on their likelihood of being prevented by an EBR system. The categories were EBR-related, uncertain and non EBR-related.

EBR-related

A deviation that is classified as EBR-related could with high certainty be eliminated if an EBR system was implemented. Examples of such deviations are missed signatures, incorrect calculations etc.

Uncertain

When a deviation is classified as uncertain it is very hard if not impossible to determine its exact cause. Most likely some of the uncertain deviations are EBR-related but this is, however, a matter of speculation.

⁹ Tablet Quality

Non EBR-related

If a deviation is certainly not reducible with an EBR system it is classified as non EBR-related. Examples of such deviation causes are machine errors, damaged incoming materials etc.

4.2.2.3 WIPV decrement

WIPV constitutes a large part of costs. When introducing an EBR system, lead-times can be shortened and WIPV thereby reduced. Current lead-times were therefore retrieved from the planning department and averaged over the first six months of 2005. Additionally, the finance department assisted with information regarding manufacturing costs for each evaluated product group.

4.2.2.4 Labour decrement

Operative Labour

To investigate the potential amount of operative labour reduction it was essential to know the scope of the batch protocol contents. Hence, a study that analysed the batch protocol contents was undertaken. The data was recorded and categorised according to Table 5.

Table 5: Data recorded in the batch protocol analysis

Batch Protocol Analysis	
Date	The current date, usually documented at the beginning of the batch protocol
Time	The current time, usually start and stop times for various processes
Article number	Previous article number being manufactured in a specific room or machine is documented
Batch number	Previous batch number being manufactured in a specific room or machine is documented
Equipment number	The equipment is identified by an identification number that is usually recorded in the beginning of the batch document
Monitored value	When an operator logs a value directly without performing any tasks to retrieve it
Measured value	When an operator performs a task to retrieve a value e.g. by weighing material
Calculation	This category is used whenever an operator performs calculations. Calculations often occur in process exchange analysis at the end of the batch protocol.
A-signature	An operator uses the a-signature to assure that correct procedures were followed when performing a task
B-signature	The b-signature is used by an independent source to ensure that an operator has performed a task correctly
Scale receipt	To ensure that correct weights are documented a receipt from the scale is attached to the batch protocol

Quality Control Labour Reduction

To estimate the amount of quality control work that is performed for each batch a study of the batch protocol flow was carried out. Mapping diagrams were drawn and labour time durations were measured. A more detailed description is given below.

When manufacturing is completed, quality personnel use the batch protocol to investigate and ensure satisfactory quality of the product. Every batch protocol is thoroughly checked by multiple instances of personnel in different levels. The process can be highly time-consuming due to complex control procedures and heavy administration. It is therefore important to know exactly which batch protocols are in use and what their routes are. The information simplifies the comprehension of information flow and quality control methods at the Gärtuna site, which are considered to be fundamental knowledge for further analysis. The batch protocol flow mapping is intended as a basis for complexity reduction and simplification of everyday work, thus, achieving cost efficiency and other benefits.

The studied manufacturing organisations use almost identical methods when checking and controlling batch protocols. This is mainly because the subdivisions of the large quality organisation at the Gärtuna site perform the primary parts of the quality control. The different subdivisions working with batch protocol analysis in the TQ organisation are assigned to specific process cells and, thus, specific sets of batch protocols. There is no work-related overlapping between the different subdivisions regarding batch protocols.

After a batch is produced and documented the batch protocol is handed in for processing. The first instance of processing is the *Operator Control*. An operator having additional training and working closely with the quality department performs the operator control. The tasks include checking that all signatures are signed accurately, calculations are performed correctly and additional documentation is in place. If there are minor production deviations these should also be reported by the operator controller.

When the operator control is completed the batch protocol is passed on to a *Quality Technician* (QT). An employee at this position belongs to the TQ department and usually has completely different training and experience. Quality technicians initially and briefly perform the same tasks as the operator controller before carrying on with more qualified quality evaluation tasks.

When a batch, belonging to a certain process cell, is produced there is a set of different batch protocols that need to be evaluated, which is performed by *Quality Assurance* (QA) staff. QA employees belong to the TQ organisation and are the last person in the chain of batch protocol controllers. Tasks performed by a QA have a tendency of being complex and demanding high qualifications and experience.

4.2.2.5 Sensitivity to disturbance

There were four different risk criteria that needed to be investigated. The PuP system was used to obtain utilisation statistics and to investigate bottlenecks in manufacturing. This data was averaged over the first eight months of 2005 in order to enhance reliability. The CoGm was acquired from the finance department and the deviations per batch values were obtained from the TPP department.

4.3 SELECTION

The first step in the selection process is to define a suitable set of candidates for the selection process described in subsections 4.3.1 and 4.3.2. As earlier described the candidates are defined as production areas dedicated for certain product groups, primarily based on production facility structure. Certain product groups can be manufactured in different production areas but this is regarded as insignificant since the Gärtuna site in general is product group oriented. A complete list of the five initial candidates is shown in Table 6. Due to confidentiality reasons the candidates cannot be referred to the product group they belong to.

Candidate A includes a large number of production areas with different product groups in the same facility. Their manufacturing procedures and production complexity are in many cases very different. However, for simplicity and relevance reasons all production areas in the facility are regarded as one in the screening process.

Candidate B concerns tablet production and nearly comprises an entire facility, which is more or less dedicated to the production area.

Candidate C and D are capsule based and located in the same manufacturing facility but involve significantly different manufacturing procedures for the granulation process. Since they indeed are separate production areas it is natural to define them as different candidates.

Candidate E concern tablet production and is exclusively dedicated to its product group. Its production process is very similar to Candidate D but primarily distinguished by other product group characteristics.

All low volume production areas in factories outside Candidate A's facility were disregarded, including production areas in Candidate B's facility.

Table 6: Candidates for the feasibility screening

Feasibility screening candidates	Type of Production
Candidate A	Tablet/Capsule
Candidate B	Tablet
Candidate C	Capsule
Candidate D	Capsule
Candidate E	Tablet

Each candidate is evaluated for every screening criterion in the subsections below.

4.3.1 Feasibility Screening

The feasibility screening is designed to remove highly unsuitable candidates from the later and more time-consuming parts of the evaluation process. The screening comprises product and equipment criteria since they are important measurements of production area characteristics. The objective is to investigate the production areas and acquire indications of problems and circumstances that make candidates inappropriate for an EBR system implementation.

4.3.1.1 Product criteria

Candidate A

The large total production volume stands for about one fourth of the total production at the Gärtuna site. The article spread is considerable although it has been dramatically decreased over the last years. The main reasons for such an action have been to lower the number of non-profitable products, mainly available for goodwill reasons, and to release capacity for upcoming products. It can be concluded that the total production volumes for Candidate A have been decreased and that it is unlikely to face any significant increase in the near future. In general the production volume per article is low and the volume trend is declining. However, some products with smaller volumes shows the opposite trend but are still regarded as low volume products.

Candidate B

The product group for Candidate B stands for approximately one third of the total production at the Gärtuna site. The article spread is relatively low and the volume is surprisingly evenly distributed on different articles. Thus, there is no significant article being particularly suited for an EBR implementation regarding production volumes. Candidate B shows a positive volume trend, which could indicate an increased future market demand.

Candidate C

The candidate stands for a small part of the total production at the Gärtuna site. Even though the article spread is low the volume per article is also low except for one particular article that stands for half of the entire capsule production volume. The volume trend is relatively stable although a slight decline can be distinguished.

Candidate D

Candidate D stands for a very low percentage of the total production volume at the Gärtuna site. A low article spread does not compensate the low production volume and hence, the volume per article is low for all articles in the production area. The production volume additionally shows a slightly declining trend.

Candidate E

The product group produced by the candidate has a large production volume standing for one third of the total production at the Gärtuna site. A low article spread yields a rather high production volume per article on average. However, there is a significant difference in this metric between articles of the product group. Apparently, one third of the article spread stands for 90% of the total production volume, which is potentially beneficial due to high volume products great impact on lead-time and financials. In addition to high production volumes a strongly inclining volume trend makes Candidate E particularly suitable for the introduction of an EBR solution.

4.3.1.2 Equipment criteria

Candidate A

Due to the great article spread, the facility for Candidate A has a large number of diverse manufacturing equipment. The standard of this equipment park varies and the age span is over 50 years. Hence, there is relatively low internal compatibility between machine types and some of them are not particularly suitable for an EBR implementation. However, the great diversity yields some external equipment compatibility.

Some equipment is connected to the PIST system but no complete production area is. The PIST integration is generally low.

Candidate B

The general manufacturing procedure involves more steps than for most other products. Even though some of these are not extensive there is a significant number of diverse manufacturing equipment. The manufacturing equipment is rather modern and have equivalent model numbers to the extent it is feasible. This yields a high internal compatibility, lower spare parts inventory and facilitation of support operations. It also somewhat affects the external compatibility positively. However, in general there is relatively low compatibility with other production areas due to specialised manufacturing procedures.

The main manufacturing equipment is connected to PIST but some instances are however not connected. In cases where a PIST connection is not critical, the EBR system should be accessed and used with the assist from e.g. new PDA equipment, in order to prevent hybrid batch documentation.

Candidate C

There is relatively insignificant diversity of the manufacturing equipment in the production area. These equipment have a relatively high age on average with low external compatibility due to the uniqueness of the manufacturing process. Some of the production equipment is tailor-made for the Candidate C production area while other machines are shared with the Candidate D production area. There is however generally a satisfying internal compatibility.

Candidate C is to a very low extent connected to PIST. Whilst some process cells belong to stand-alone systems others lack SCADA terminals.

Candidate D

Candidate D uses modern equipment with low diversity. In addition to the similarity with the Candidate E production area Candidate D has a significant scalability advantage. The granulation manufacturing for capsules and tablets are almost identical, which gives the equipment high external compatibility. In combination with high internal compatibility this yields high overall scalability potential of an EBR solution for Candidate D.

An almost complete PIST integration further makes the production area suitable for an EBR solution from an equipment analysis perspective. The only significantly weak point is the capsule filling machines, which in some cases have deficient PIST integration.

Candidate E

The production area uses modern equipment with very low diversity. As mentioned earlier, the area has high external compatibility with Candidate D and to some extent also with Candidate A and Candidate B. The internal compatibility is additionally very high, yielding a substantial scalability potential of an EBR solution.

Furthermore, an almost complete PIST integration makes the production area suitable for an EBR solution from an equipment analysis perspective.

4.3.1.3 Summary

A summary of the feasibility screening is displayed in the Table 7 below. The colour scheme describes the suitability and potential of implementing an EBR system on the candidate. Green colour implies high suitability and benefit gain. Yellow colour implies that it might be suitable and beneficial and red colour suggests that the candidate is likely to be unsuitable and unbeneficial for an EBR implementation.

Table 7: Summary of feasibility screening of the candidate production areas for EBR implementation

Criteria type	Product			Equipment		
Criteria group	Product importance and suitability			Technical suitability	Scalability	
Criteria	Relative volume	Volume trend	Article spread	MIS integration	Equipment standard	Standardisation
Candidate A	High	Down	High	Medium	Low	Low
Candidate B	High	Up	Medium	Medium	Medium	Medium
Candidate C	Low	Slightly Down	Medium	Low	Low	Low
Candidate D	Low	Slightly Down	Low	High	High	High
Candidate E	High	Up	Low	High	High	High

It was obvious to reject Candidate A and Candidate C from the candidate list. These candidates showed least potential according to both product and equipment related criteria.

The main reasons for not selecting Candidate A concern a very high article spread, a high equipment diversity and a mediocre PIST integration. The decline in production volumes further contributed to the decision.

Candidate C was discarded due to several different reasons. The PIST integration is deficient and the manufacturing processes and equipment are outdated. The candidate also has a low declining production volume, which indicates that the benefit gains from an EBR implementation might not be substantial. The remaining candidate list for the risk-return screening is presented in Table 8.

Table 8: Remaining candidates after the feasibility screening

Risk-return screening candidates
Candidate A
Candidate B
Candidate C
Candidate D
Candidate E

4.3.2 Risk-Return Screening

The risk-return screening selects the most promising of the feasible candidates for an EBR system implementation. The screening comprises economic and risk criteria since they are important measurements of a candidates potential to successfully implement a profitable EBR system. In order to evaluate whether or not it is financially beneficial to introduce an EBR system to the most promising candidate a detailed business case should be performed. However, this is out of the master thesis projects scope.

4.3.2.1 Economic criteria

Candidate B

Candidate B has a medium amount of scrap value in relation to the other candidates. Much of these costs are likely to be reduced with an EBR system. The candidate has a high level of deviations that are EBR-related, similarly to the other remaining candidates, which indicates a high potential for reduction of deviations.

The product group for Candidate B has a high total value of production volume as expected due to its substantial production volume. The production lead-time is at a medium compared to the other candidates. However, there is still a relevant WIPV decrement potential in this production area.

The batch protocol for producing the product group is noticeably extensive and requires considerable amounts of operative labour to document. In combination with total production volume the operative labour reduction potential is regarded as substantial.

Candidate D

The candidate has very low amounts of documented scrap costs. This could be related to its low production volume but it is more likely that it is caused by faulty classification. The reasons for the faulty classification could be that Candidate D and Candidate E share a process cell and scrap costs could therefore be allocated to Candidate E rather than Candidate D.

Candidate D has the lowest lead-time of all candidates and has a low value of production volume. Hence, the candidate shows least potential to reduce WIPV.

The batch protocol for Candidate D contains a medium amount of documentation compared to the other batch protocols. Together with a low production volume this implies a low potential reduction of the total operative documentation and quality control labour.

Candidate E

The candidate has large documented scrap costs compared to the other candidates. This indicates a substantial gain if an EBR system was implemented in this production area.

The production area has a relatively low lead-time but not significantly different from the other two candidates. However, a high value of production volume indicates that a large WIPV decrement could be yielded by an EBR implementation.

The batch protocol for the candidate contains an average amount of documentation compared to the other candidates. However, in combination with its high production volume the total labour reduction concerning documentation and quality control can be regarded as high.

4.3.2.2 Risk criteria

Candidate B

The production area has a medium overall equipment utilization compared to Candidate D and Candidate E. It also has spare capacity in production, which is positive from a risk perspective. There is, however, a bottleneck in one of the processes that could cause problems if production disturbance emerged. The process is also time-consuming and critical, which could be costly if an EBR system was implemented and became incapacitated.

The CoGm is low, which indicates a relatively low risk of facing high scrap costs in the EBR implementation phase.

A potential problem source is the candidate's relatively high amount of deviations per batch. This indicates that either the process or product could be especially sensitive to disturbance. In combination with the candidate's large production volume, the risks of high scrap costs should be considered.

Candidate D

The candidate has a medium to low overall equipment utilization compared to Candidate B and Candidate E. It has no apparent bottlenecks and there are also opportunities of allocating some of the manufacturing to identical process units in the Candidate E production area if disturbance were to emerge.

The CoGm is at an average level and it has a medium to low amount of deviations per batch compared to the other candidates. These factors together indicate robustness to disturbance. If its total production volume is regarded the hazard of facing high scrap and deviation costs are limited.

Candidate E

The overall equipment utilization of the production area is medium to high compared to the other candidates. However, there are bottlenecks in process cells that could be costly if disturbance occurred. Fortunately production can be allocated to identical process cells in other production areas at the site, which reduces the implication of a manufacturing disturbance.

A relatively high CoGm is partly compensated by a low level of deviations per batch, which could indicate robustness in the production area. However, if combined with its high production volumes the risks of high scrap costs must be regarded.

4.3.2.3 Summary

In the risk-return screening the remaining candidates are evaluated regarding economic and risk criteria to decide which candidate is most suitable from a risk-return perspective for an implementation of an EBR system. Generally, there are criteria influencing each other and it can sometimes be a combination of multiple criteria that together decide a candidate's suitability regarding a single criteria. Different criteria also have different impact on the screening result.

Economic criteria are often heavily dependant on production volume. For instance, a candidate with high production volume and low profitability margin is often more profitable than a candidate with low volumes and high profitability margin. Additionally, the costs reduced by an EBR system typically concerns deviations, scrap, labour and lead-time. The magnitude of these reductions is almost proportional to the production volume, which makes the production volume factor very significant.

This master thesis project regards the risk criteria as being less critical in the selection process than the economic criteria. The risk criteria are closely dependent on utilization metrics, which are primarily concerned for the development of a successful implementation strategy. It is very important to be aware of risks and recognise them so that these can be avoided through the use of a structured and well-planned implementation strategy.

A summary of the risk-return screening is shown in Table 9. Candidate A and Candidate C are disregarded from this screening since they were considered unsuitable for an EBR implementation by the feasibility screening. This left three remaining candidates for analysis regarding economic and risk criteria.

Table 9: Risk-return screening of the remaining candidates from the feasibility screening

Criteria type Criteria group	Economic							Risk			
	Scrap decrement	Deviation decrement		WIPV decrement		Labour decrement		Sensitivity to disturbance			
Criteria	EBR related scrap	EBR related deviations	Uncertain cause	Value of production volume	Lead-time	Operative labour	Quality control	Utilization	Bottlenecks	COGM	Deviations per batch
Candidate A											
Candidate B	Medium	High	High	High	Medium	High	High	Medium	High	Low	Medium
Candidate C											
Candidate D	Low	High	High	Low	Medium	Medium	Low	Medium	Medium	Medium	Medium
Candidate E	High	High	High	High	Medium	Medium	High	High	High	High	Medium

Candidate D has high technical suitability, and is considered to be a low risk implementation alternative. The economic criteria are, however, heavily influenced by the low production volume, which gives a rather low cost reduction. Since the costs for the EBR implementation is regarded as relatively constant for the different candidates, the EBR system would be less beneficial for Candidate D and it is therefore considered unsuitable as an EBR implementation alternative.

Candidate B has fairly high technical suitability with a decent PIST integration. It is produced in a very high volume, which positively influences the economic criteria. However, the production volume is slightly declining. There are considerable amounts of documentation and quality control labour that can be reduced. The risks are considered at a medium to high level compared to the other candidates and the candidate is considered to be the next best alternative for an EBR implementation.

Candidate E has a very high level of technical suitability, its PIST integration is excellent and the equipment has low diversity. The production volume is very high and strongly inclining, which gives a solid basis for extensive long-term cost reductions. The risks are, however, considered to be high due to some bottlenecks in production and a relatively high overall utilisation. This can though, as earlier explained, be avoided by identifying the problems and take measures against them in the implementation strategy. Candidate E is therefore regarded as being the most promising candidate for an EBR implementation.

Table 5: Remaining candidate after the risk-return screening

EBR pilot project candidate
Candidate A
Candidate B
Candidate C
Candidate D
Candidate E

5.0 DEVELOPMENT OF EBR SOLUTION

The development of the EBR solution was performed in two primary steps as described in subsection 1.5.3. The first step involved a detailed manufacturing information flow analysis facilitating a manufacturing system identification process. The outcome of the identification process was a complete map of all systems communicating directly with the batch protocol. These complement the continuous mapping of manufacturing systems to complete a current AstraZeneca MES model.

The second step was to develop a theoretical EBR solution with respect to current systems and given constraints. The EBR solution is thereafter analysed regarding its benefits and detriments and its functionality is mapped onto the AstraZeneca MES model.

5.1 DETAILED INFORMATION FLOW ANALYSIS

A detailed information flow analysis enables successful identification of important systems and information flow content that should be an integral part of an EBR solution. Hence, the information flow in the Candidate E production area was mapped and analysed. The focus was primarily on information flow directly related to batch documentation, particularly concerning the batch protocol. The information flow was mapped according to the example shown in Figure 14. Due to confidentiality reasons the complete information flow mapping cannot be presented in the master thesis report.

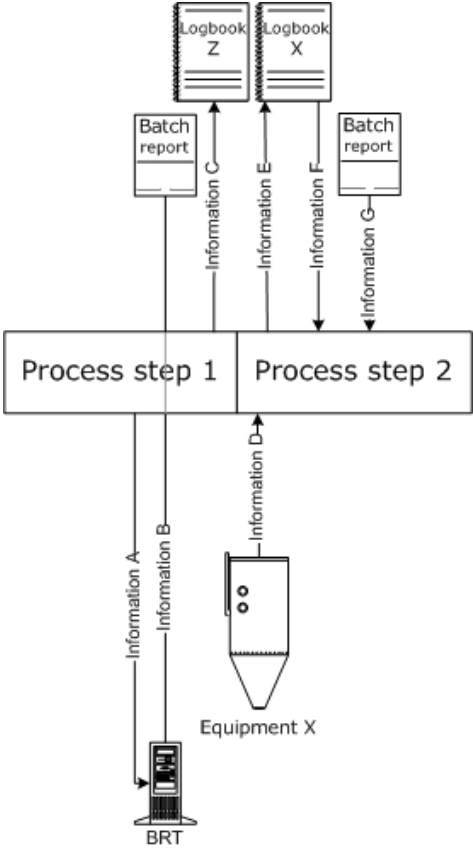


Figure 14: Information flow analysis example

An emphasis was put on mapping the actual workflow performed by the operator rather than the theoretical workflow. As mentioned earlier, the mapping is centralised around the batch protocol and its workflow. The workflow is divided into several steps, which carry the same name as in the batch protocol. The information arrows contain information descriptions, origins and destinations. For example, if an arrow points from the logbook to the batch

protocol stating information y, it means that information y was read from the logbook and documented in the batch protocol.

When the information flow mapping was completed it was straightforward to identify the systems directly involved. There are many different systems communicating with the current batch protocol, both paper and electronic based system. These types were separated in the maps, allowing for an easier analysis of a single system type. A functional grouping of the current systems is shown in Figure 15. Each group is discussed in detail in the sections below.

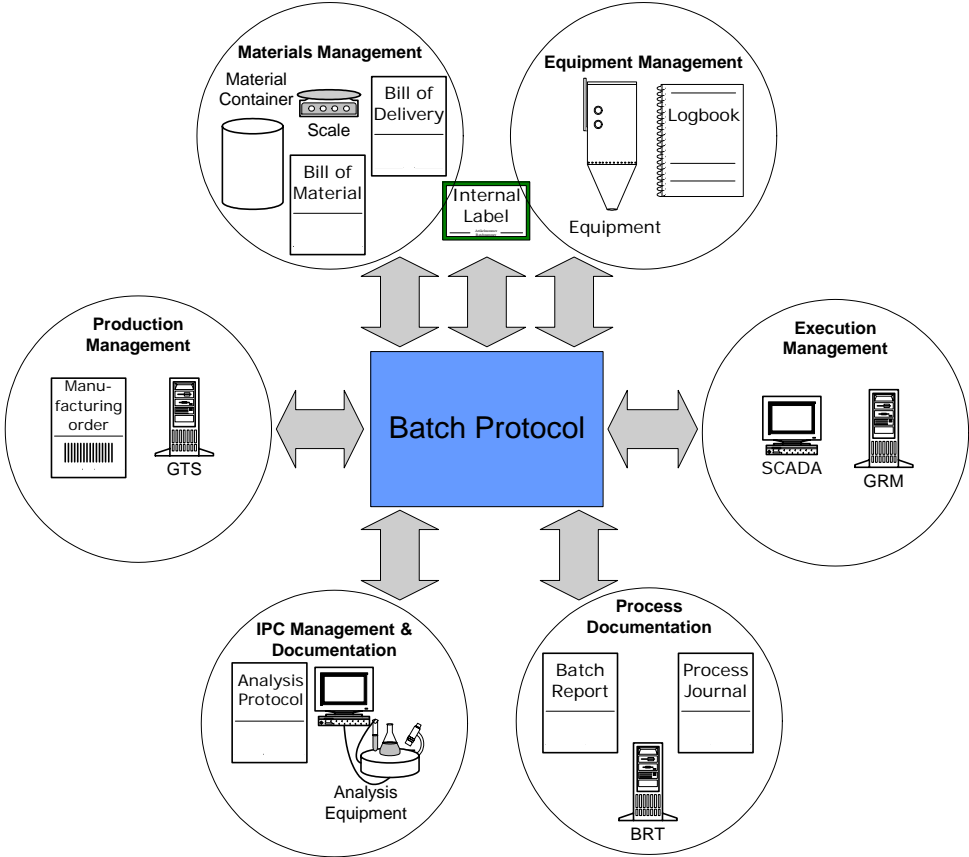


Figure 15: Functional grouping of current systems used in the manufacturing process at the Gärtuna site

5.1.1 Production Management

GTS – Gärtuna Tillverknings System

The main manufacturing system is, as explained earlier, used to handle manufacturing orders and to keep records of produced batches.

Manufacturing Order

The manufacturing order is generated from GTS by the local planning department and is thereafter placed in the Kanban queue rack. The manufacturing order specifies which article and batch to be produced. In some cases the manufacturing order also lists admixture materials for the batch, which can be used in the control of incoming materials. The manufacturing order is additionally equipped with a barcode that can be used for identifying article and batch numbers. When a batch is manufactured, the manufacturing order is appended to the batch documentation.

5.1.2 Materials Management

Scale

When the actual manufacturing process is completed scales are used to measure the produced quantities. The quantities are for example used to report material quantities in GTS and to compute material exchanges. The scales are additionally used to control quantities of incoming material. In many cases printed receipts from the scales are attached to the batch documentation to assure that the correct quantities have been recorded.

Bill of Materials

When admixture material is transferred from the warehouse to production a bill of materials physically follows it. The bill of material states which material is sent and comprises article numbers, batch numbers and quantities of the material. Additionally, the article and batch number of the destination product is specified. The bill of materials is an essential resource in the process of controlling incoming material since it is compared to the manufacturing order and labels on containers of incoming material. After a batch has been produced the bill of materials is added to the batch documentation and further used for validation purpose.

BoD – Bill of Delivery

The planning department prints the bill of delivery before the manufacturing starts. It is then placed together with the manufacturing order and the batch protocol in the Kanban queue rack. The bill of delivery is similar to the bill of materials and serves as a table of contents for the material, which it physically follows. When an article is manufactured and put into containers it is equipped with the bill of delivery. The information it carries includes article number, batch number and quantity of the produced goods. The bill of delivery is predominantly used internally but also externally for produced goods that are sent to the warehouse. When incoming material carries a bill of delivery it is appended to the destination batch documentation after the destination batch is produced.

Internal Label

The planning department prints the internal labels ahead of time and places them together with the rest of the initial batch documents in the Kanban queue rack. The internal labels are put on the containers of finished goods, in the logbook, on manufacturing equipment and on test samples. The printed information on the labels only contain the article number of the end product, additional information such as batch number is usually written by hand on the labels.

5.1.3 Equipment Management

Equipment

All equipment carries an id-number, which is used as a unique identifier. The equipment id-number is documented in the batch protocol and in the logbook for traceability reasons.

Logbook

There are two types of logbooks, machine specific and area specific. The significant content in the different logbooks is very similar and they are in that aspect regarded as identical. Every machine and area is associated with a specific logbook containing manufacturing related information. The information concerns usage, setup and sanitation of the machine or area. The different operations are linked to the responsible operator identity and the date and time of the operation execution. This information is used to keep track of machine/area usage, setup and sanitation. Furthermore, some of the information is taken from the logbook and documented in the batch protocol.

5.1.4 Execution Management

SCADA – Supervisory Control and Data Acquisition

The SCADA has a close relation with manufacturing equipment and contains instructions for process control. There is usually customised software, which is machine specific, installed on the SCADA. The software is used for managing processes, controlling article and batch numbers and communicating with the GRM system. Some of the content stored in the SCADA is documented in the batch protocol.

GRM – General Recipe Manager

The operator uses the general recipe manager to download manufacturing recipes to the SCADA. A special GRM client implemented in the SCADA software is used to access the recipe.

5.1.5 Process Documentation

Batch Report

The batch report is a fundamental part of the batch documentation and is already accessible in an electronic format. The quality department also use the batch report to inspect production processes after manufacturing.

BRT – Batch Report Tool

The operator uses the Batch Report Tool system to generate batch reports.

Process Journal

The process journal is generated by the planning department and placed together with the rest of the initial batch documents in Kanban queue rack. During manufacturing, the process journal is used to document important process values such as temperature, pressure and humidity. After the batch production is completed, the process journal is appended to the batch documentation.

5.1.6 IPC Management & Documentation

Lab Equipment

Operators usually test the products during manufacturing by using IPC. When performing these tests the operators rely on lab equipment such as scales, sieves, and sophisticated computers to produce test results. The result from the lab equipment is usually recorded in the batch protocol and a more detailed description and verification of the test is recorded in a separate appendix, such as an analysis protocol. The lab equipment carries id-numbers, which are recorded in the batch documentation.

Batch Protocol for Quality Control

The batch protocol for quality control is generated by the planning department and placed together with the rest of the initial batch documents in the Kanban queue rack. During some manufacturing processes, the product is continuously tested and the batch protocol for quality control is used to document important test parameters such as weight, size and appearance. After batch manufacturing the protocol is appended to the batch documentation.

Analysis Protocol

The analysis protocol is generated by local operative staff and is used for documenting some of the IPC tests. The analysis protocol contains article number, batch number and analysis parameters. The results of the analysis are usually documented in the batch protocol. After the analysis is finished the analysis protocol is appended to the batch documentation.

Test Protocol

The test protocol is generated from analysis equipment for some of the IPC types. The protocol contains parameter values from the test carried out by the equipment. The protocol also contains article number and batch number for the tested product. The test results are usually recorded in the batch documentation and are sometimes used for computations. When the testing is finished the test protocol is appended to the batch documentation.

5.1.7 MES Mapping

A mapping of the current manufacturing systems to the ISA 95 MES model¹⁰ is shown in Figure 16. Additionally, the EBR model defined in subsection 2.3 is presented in the background by a yellow colour. Current PIST systems are coloured blue, quality control equipment and systems in light yellow, general existing systems in green and complementary manual systems in red. However, the map does not reveal whether or not a complete MES functionality is covered by the existing systems.

¹⁰ Due to project constraints only the production view was examined in the ISA 95 MES model.

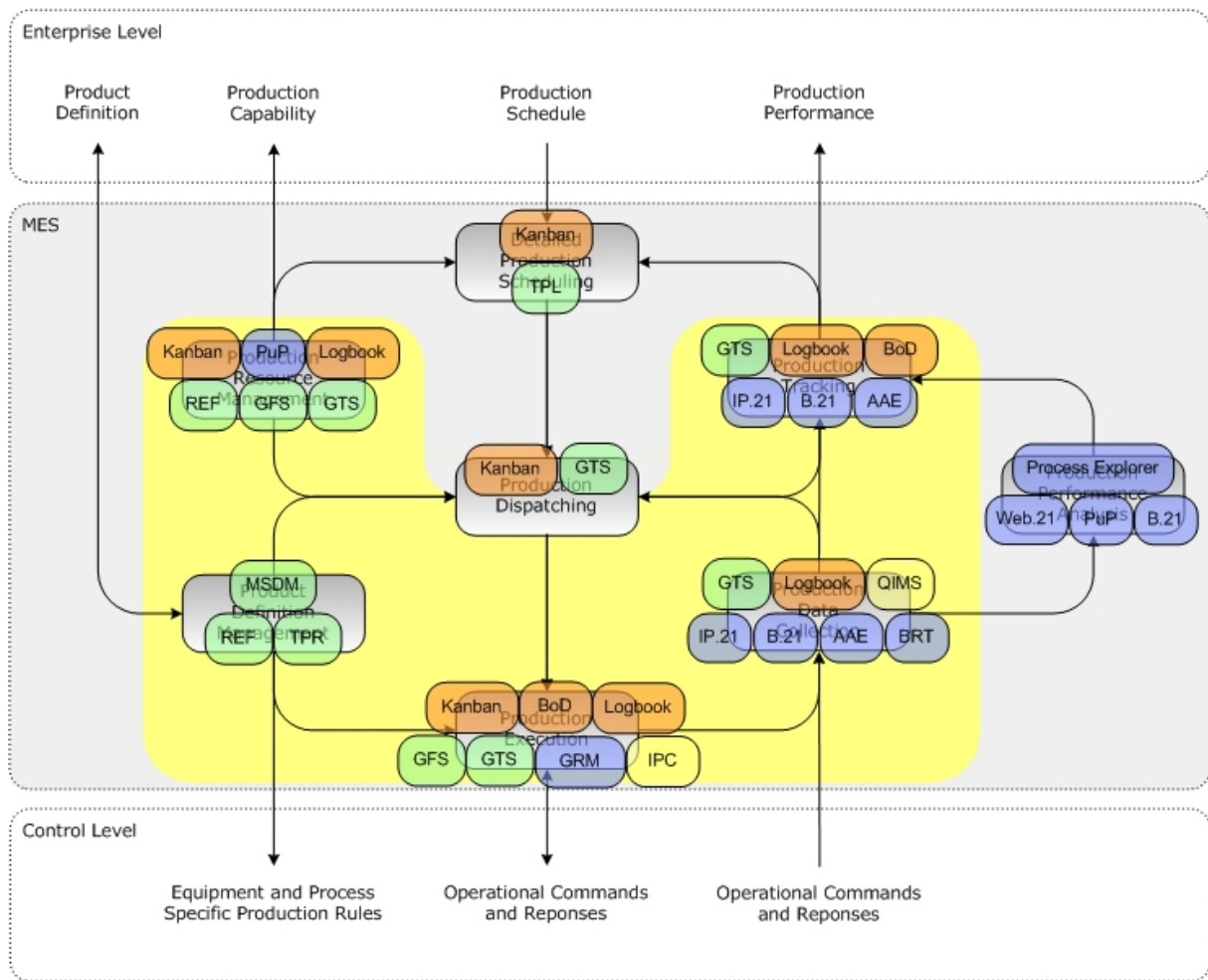


Figure 16: MES and EBR mapping of current systems with a focus on the ISA 95 production view.

Most of the MES functionality regarding *Product Definition*, *Production Tracking* and *Production Data Collection* is captured by the current systems. *Production Resource Management* functionality is well covered by the current systems even though there is an extensive use of manual logbooks, which preferably are replaced by electronic substitutes in a complete EBR system. Due to the Kanban scheduling system, much of the *Detailed Production Scheduling* and *Production Dispatching* functionality is not supported. Moreover, workflow management constituting a significant part of the *Production Dispatching* and *Production Execution* activities is not supported at the Gärtuna site today. Finally, the current systems need minor complementary of *Production Performance Analysis* functionality in order to cover the entire activity.

Regarding the given project constraints to disregard scheduling¹¹ and quality control systems the primary concern from an ISA 95 perspective would be to introduce workflow management functionality. Additional *Performance Analysis* functionality is not regarded as critical for general manufacturing system performance and is therefore of secondary concern. Hence, an EBR solution should principally focus on the introduction of an electronic logbook and workflow management functionality. It is also important to evaluate the possibility to increase communication between activities and systems. Much work is performed multiple times by different systems, which is regarded as ineffective use of resources.

¹¹ A remark is that the scheduling activities most likely could be sincerely improved by the introduction of a more advanced scheduling system.

5.2 EBR SOLUTION

By analysing current manufacturing systems and procedures it is possible to establish necessary conditions and infrastructure for an EBR solution. The information flow between systems must sometimes be assisted by additional interfaces, which is explained further in the subsections below. There are also several constraints that need to be considered and accounts must be taken to current as well as new systems. The main components interacting with the EBR solution are shown in Figure 17 below. This is a schematic transformation of the systems described in Figure 15 into an EBR solution regarding project constraints, planned system introductions and conclusions from subsection 5.1.7.

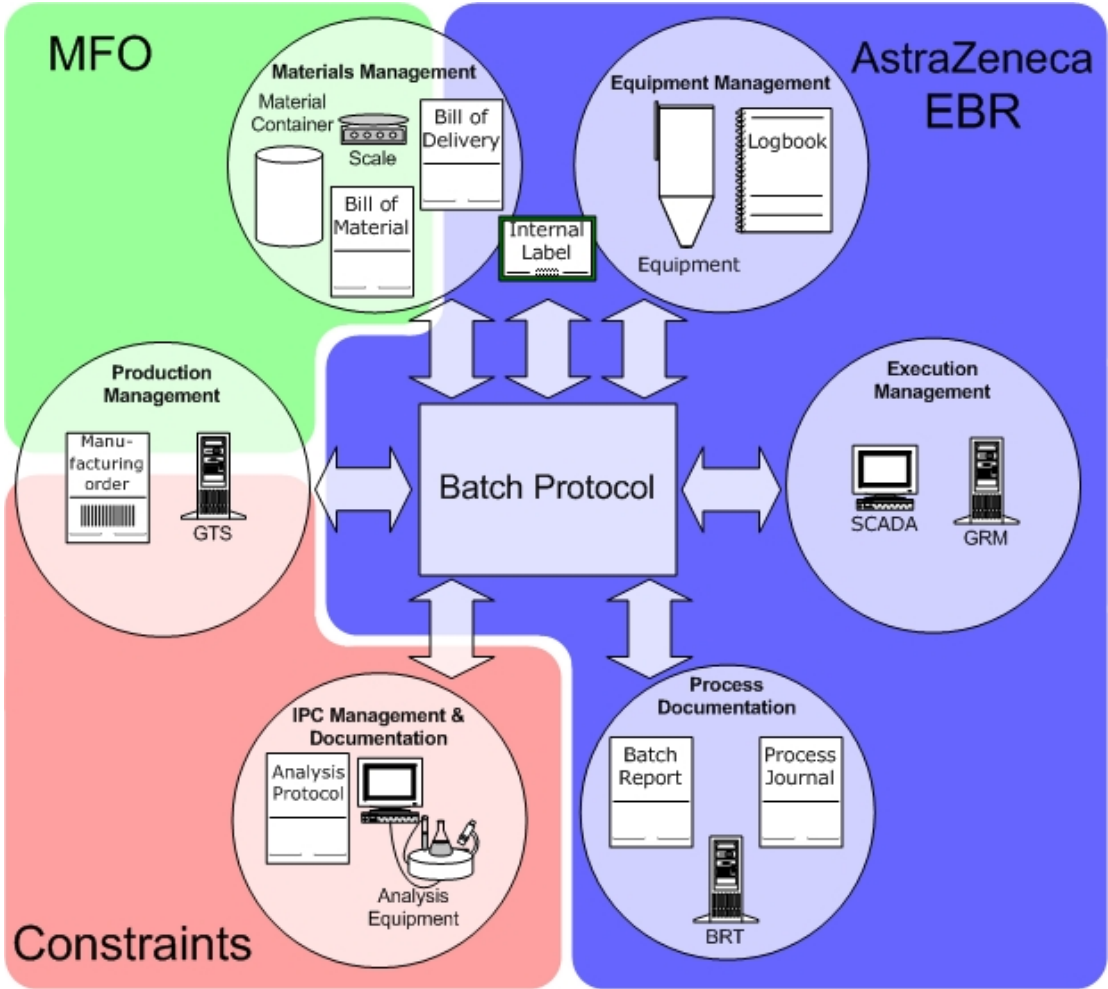


Figure 17: Summary of main systems included in the AstraZeneca TPS EBR solution

5.2.1 Involved Systems

Many current systems either constitute a natural part of an EBR solution or contain parts that are affected by an EBR introduction. Most new systems are connected to the PIST network, which is built on fast fibre optics. The additional components needed to complete the EBR system would preferably be a part of the current PIST network. However, the older systems at the Gärtuna site are connected to the network *ASTRAN*, which is slower than PIST. Most likely, the two networks are connected during the next year. This could become a problem since *ASTRAN* already has difficulties handling data traffic from the current systems. An introduction of an EBR system would significantly increase the data traffic over the *ASTRAN* network, which might be overloaded. This can however be solved by using the network *AZIA* for communication handling. Current systems affecting the EBR solution are further discussed under the topics below.

InfoPlus.21

Since IP.21 contains important batch data it is included as a natural part of an EBR system. The IP.21 will be accessed through an interface to PIST. However, the process analysis applications Process Explorer and Web.21 are not included in the EBR solution. This functionality is certainly useful to incorporate in a MES but should not be included in an EBR system.

Oracle

The Oracle database contains vital information for an EBR solution. However, some of the applications associated with the database should not constitute a part of the EBR solution. One of these applications is BRT that is used to create and print batch reports. This particular application is not likely to be very useful with a complete EBR system since the batch report preferably should be integrated with the batch documentation. Naturally, the intelligence included in BRT is better suited for the EBR solution.

Batch.21 is included as a natural part of the EBR system since it contains vital batch specific data. Another important part of the Oracle database, which needs to be added, is the AspenTech AE scheme.

It could be useful to include AspenTech's *Event.21* application in the EBR system, as it would simplify the handling of alarms and events. With an electronic batch record it would not be efficient to comment run-time alarms on paper, as currently done. Event.21 enables a solution that stores an electronic comment from the operator with the correct alarm or event.

Both the IP.21 and the Oracle database comprise a part of the PIST network. If the EBR solution would be a part of the PIST network, the design of IP.21 and Oracle interfaces is limited to database communication within a single network.

MSDM – Manufacturing Site Document Management

As earlier explained, the MSDM database contains important routines and procedures used in manufacturing operations. This information is needed by the EBR solution and there are primarily two different approaches for the EBR solution to assimilate the information. The first approach is to let the EBR solution communicate with the MSDM database and the other is to include some of the routines and procedures in the EBR system. The first approach is regarded as inferior to the second since it involves large amounts of communication between different systems and potentially very complex routine update procedures when cascading updates may need to be performed in different systems. Some of the routines might also be transferred into program code for controlling manufacturing procedures. If a routine is then updated, the program code must also be updated which becomes exceedingly complicated in the first approach.

MFO – Manufacturing Operations

The current GTS system will in the near future be replaced by another system, *Manufacturing Operations* (MFO). MFO will be based on GTS but additionally have functionality for materials management performed by barcode scanning. MFO will also manage scales and weighing procedures.

MFO is responsible for delivering manufacturing orders to operative staff and the system stores batch specific data such as manufacturing times and quantities. MFO is also responsible for the transactions and control of arriving and departing material. It is not necessary to include the MFO system in the EBR solution but certain parts might be needed to ease the communication process.

MFO will be accessed through the network AZIA, which complicates the interface design since two different networks are involved in the communication process.

SCADA

Most of the process values are stored in the IP.21 database. However, some data is also stored locally on the SCADA. For instance manufacturing recipes for the tablet compression machines are typically stored locally on the SCADA rather than in the GRM. The SCADA is additionally responsible for forwarding process values from the equipment sensors to the IP.21 database. Such information passing makes use of *MQ Series* software and *iFIX* scan nodes.

It is preferable that the operator uses a single interface to communicate with all components in the EBR system. SCADA computers should therefore be adapted to the EBR solution. The EBR system should be able to partly control the SCADA by the use of push and pull operations. The interface for carrying out such procedures might preferably use the scan nodes for intersystem communication. The SCADA software further complicates the process since considerable amounts of customisation work is necessary.

5.2.2 EBR Infrastructure

Systems that constitute important parts in any EBR system concerning process execution, documentation and analysis have already been implemented at the Gärtuna site. It is, however, determined that additional parts and infrastructure is needed in order to form a complete AstraZeneca TPS EBR system. When the communication with current and new systems is established, the additional components of the EBR system needs certain predefined internal parts to function properly. The main functionality was identified in subsection 5.1.7 as being particularly important for an AstraZeneca EBR system to focus on. A summary of these parts and their internal and external communication is presented in Figure 18. The new parts are highlighted with a blue background and are defined and discussed further in the text below. A detailed study of process execution and control is out of the project's scope but it is recommended to consult the standard ISA 88 Part 4 if such an analysis is undertaken.

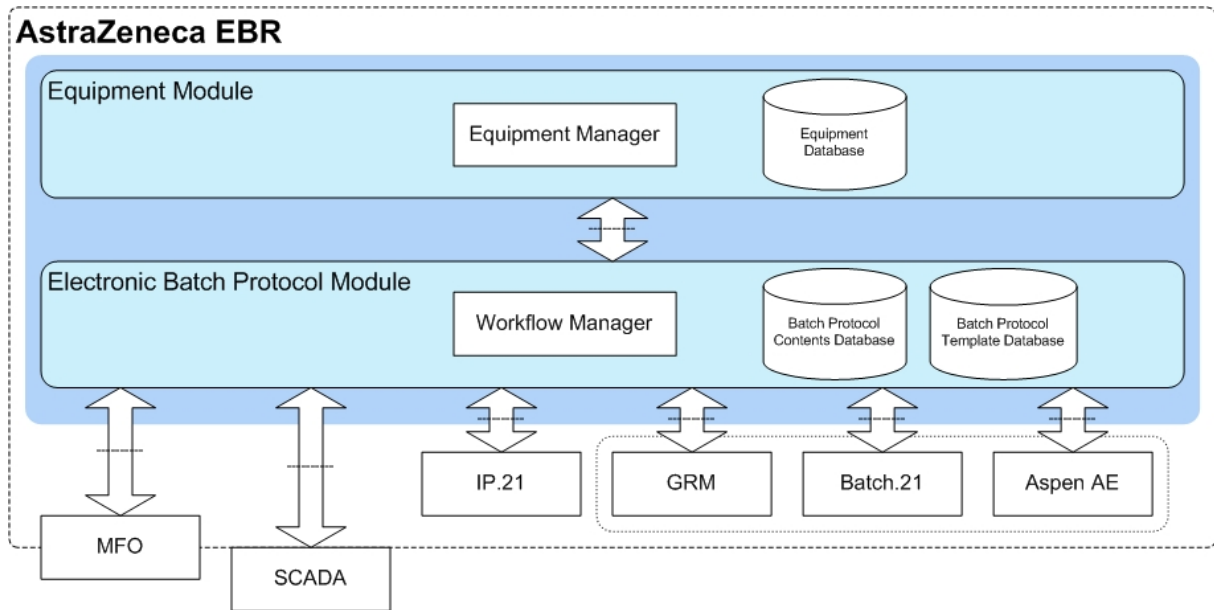


Figure 18: EBR solution infrastructure and interfaces

Electronic Batch Protocol Module

As seen in Figure 19 the central part of the *Electronic Batch Protocol Module* (EBP) is the workflow manager, which incorporates workflow management functionality. The workflow manager has many important tasks and handles communication with other systems such as MFO, SCADA and PIST-related systems through different interfaces. The workflow manager also handles communication with the *Equipment Module*, which is later described in more detail.

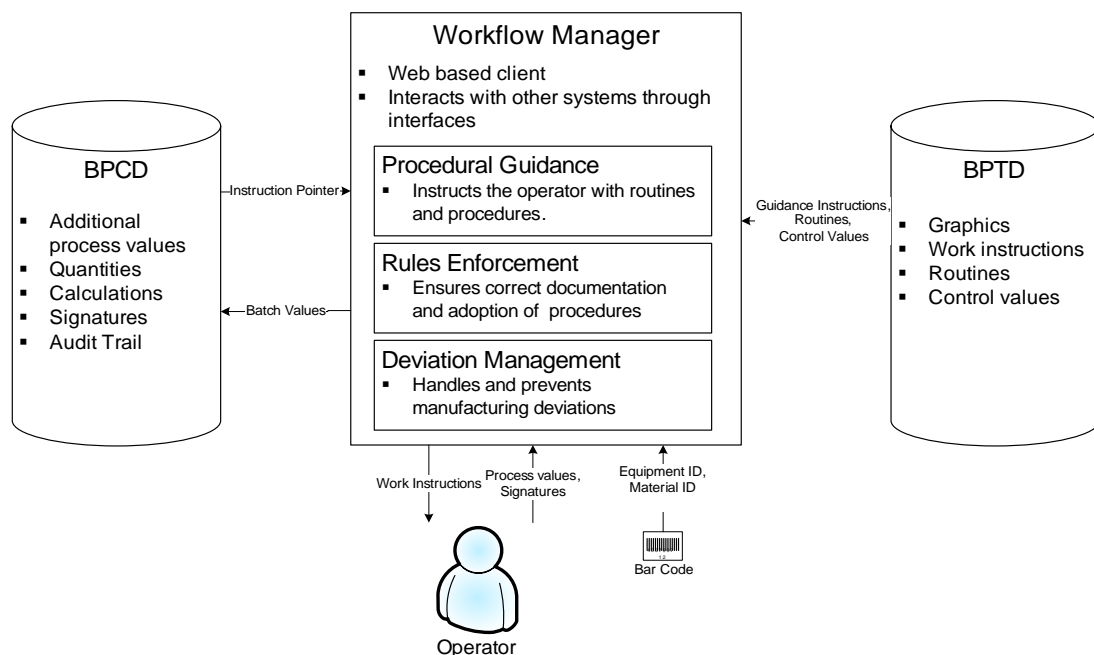


Figure 19: Electronic Batch Protocol Module structure

To assist the workflow manager there are two databases in the Electronic Batch Protocol Module. The first database contains all batch protocol template information such as graphics, desired process values, program code, routines and instructions. The database is in this project referred to as the *Batch Protocol Template Database (BPTD)*. Routines and procedures regarding manufacturing currently located in the MSDM database are moved to the BPTD for reasons earlier stressed. Some of the program code used to control manufacturing is based on these routines. Consequently, if the routines are updated the program code is also updated. This eliminates much of the parallel work associated with handling SOPs and routines. It also reduces the risk of having inconsequent information in the batch protocol compared to SOPs or routines.

The second database is referred to as the *Batch Protocol Contents Database (BPCD)* and contains batch specific data related to the BPTD. The stored data is needed to make the batch documentation complete according to regulations. The data includes batch values not stored in the IP.21 and Oracle databases, such as equipment id, additional process values, signatures, quantities and timestamps. The BPCD also contains other batch protocol specific information such as batch protocol position pointers and audit trail. Additionally, information communicated from the MFO system, such as manufacturing quantities and verification signals, is stored in the BPCD.

One of the most important tasks for the workflow manager is to interact with the user through a user interface, which preferably is web based. This involves giving the user instructions and accepting input values from the user and other systems during the manufacturing process to verify that correct procedures are adopted. Such a procedural guidance function controls manufacturing procedures, manufacturing rules and material specifications. Instructions can be given to the user in a format similar to the Batch Protocol currently deployed at Gärtuna.

The rules enforcement function ensures that the manufacturing procedures are adopted correctly and that the batch is documented in a FDA compliant way. Process values and quantities are compared with pre-defined values to establish that manufacturing is performed according to its definitions and rules. The incoming values from the operator during run-time, such as signatures and additional process values are stored in the BPCD and compared with values from the BPTD. Furthermore, the rules enforcement function performs certain calculations and other data processing being important parts of the batch process analysis.

The deviation management function has the ability to manage deviations as they occur and can in some cases prevent deviations from occurring. Such a control compares real-time manufacturing data with production constraints and interacts with the procedural guidance function to give the user appropriate instructions, e.g. if there are process deviations the workflow manager could guide the user through the correct routine procedures.

Equipment Module

The Equipment Module shown in Figure 20 is intended to be an electronic replacement for the existing logbooks. Thus, the Equipment Module is used to handle equipment use, sanitation and setup. The module also handles communication with operators, quality personnel and the EBP workflow manager. Its infrastructure constitutes of a database management system with different interfaces for different users.

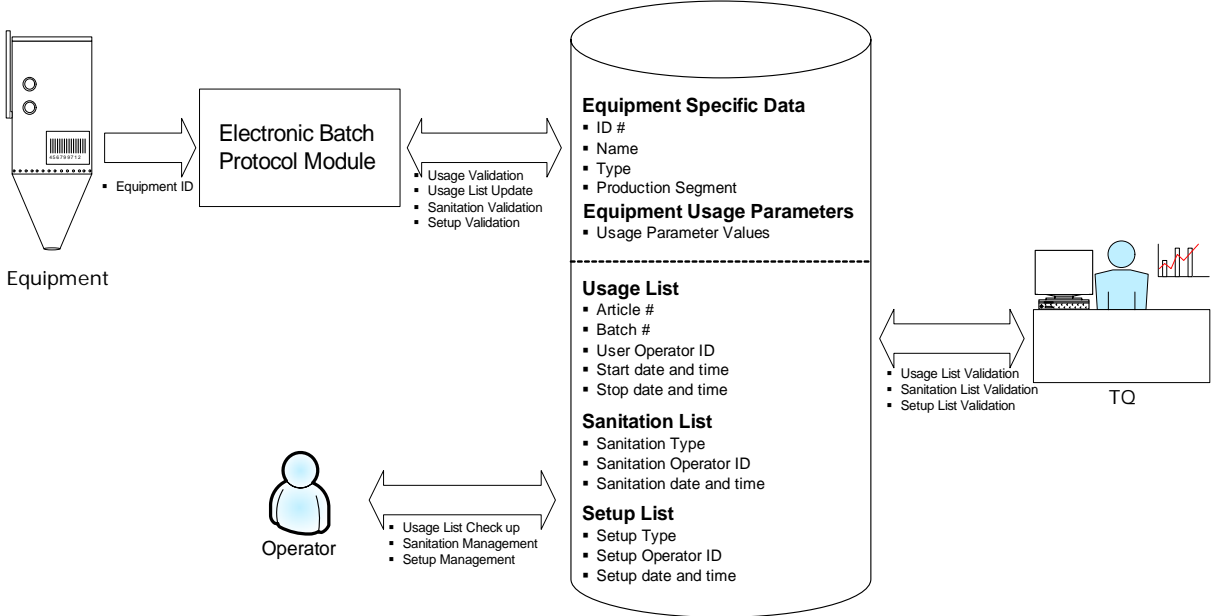


Figure 20: Equipment Module structure

The databases management system stores equipment specific usage, which is linked to a certain equipment id-number, article number, batch number, operator and time. The workflow manager in the EBP mainly initiates the information storage but it is also possible to make manual alterations to the database. The most preferable method of identifying equipment is through barcodes mainly due to its capability of reducing manual errors. However, it should also be possible to identify equipment manually. Operators may find the usage list a helpful tool when scheduling serial production (campaigns) on equipment. Quality personnel can also access the usage list through a special interface to trace manufacturing.

Sanitation management is an important issue from a quality perspective. The Equipment Module has built in functionality for this purpose. The operator is able to manage sanitation through a special interface and it is possible to store equipment id, sanitation type and time in the database. The Equipment Module can also help the operators to schedule sanitation and notify ahead of time if some equipment needs to be sanitised. The workflow manager is able to access the sanitation list to ensure that the equipment status is compliant with regulatory demand before initiating the manufacturing process. Quality personnel can also validate the equipment sanitation status and compliance through a special interface.

The Equipment Module also stores information about necessary setup procedures performed on equipment. Operators can access the setup information through a special interface. The setups are associated with an equipment id, type, operator and time. The workflow manager is able to access the setup data to ensure that the equipment status is compliant with regulatory demand before initiating the manufacturing process. Quality personnel can also validate the equipment setup status and compliance through a special interface.

5.2.3 EBR Benefits and Detriments

There are many benefits and detriments that come naturally when introducing an EBR system. Information is collected more rapidly and in a much larger quantity. Information becomes more accessible to systems and staff, which enable an increased in automated and more effective control and verification process. This allows for a significant reduction of labour, lead-time and process deviation related costs. However, some costs are likely to increase with an EBR system, e.g. data record costs and system caused deviation costs. The previously added EBR components and their benefits and detriments are presented in Table 10.

Table 10: Summary of the EBR components and their benefits and detriments

EBR Component	Benefit Area	Detriment Area
<p>Workflow Manager The workflow manager incorporates procedural guidance, rules enforcement and deviation management. The user is guided through important procedures and steps following routines and manufacturing rules. Unexpected events, such as process deviations, can be handled in real-time and perhaps also prevented.</p>	<ul style="list-style-type: none"> ▪ Manufacturing Deviations ▪ Scrap Cost 	<ul style="list-style-type: none"> ▪ Complex Routine Procedures ▪ Inflexible Production
<p>Batch Documentation Data Collection Information intended for the batch documentation is collected by the EBR system and is available for processing. The workflow manager and the BPCD perform this task.</p>	<ul style="list-style-type: none"> ▪ Traceability ▪ Automated Manufacturing Quality Control ▪ Storage Cost 	<ul style="list-style-type: none"> ▪ Data Record Costs ▪ Data Accessibility
<p>Equipment Module The Equipment Module implements an electronic logbook function. Data concerning manufacturing, sanitation and setup is recorded.</p>	<ul style="list-style-type: none"> ▪ Equipment Statistics ▪ Traceability ▪ Deviations 	<ul style="list-style-type: none"> ▪ Data Record Costs ▪ Data Accessibility
<p>Paperless Production The use of an EBR system makes paper based documentation and instructions obsolete. Important instructions and batch documentation data regarding quantities, procedures, process values and times are managed electronically.</p>	<ul style="list-style-type: none"> ▪ Documentation Deviation ▪ Lead-times ▪ Documentation Labour ▪ Storage Cost 	<ul style="list-style-type: none"> ▪ Data Record Costs ▪ Data Accessibility
<p>System Integration The structure of the EBR solution integrates currently isolated production systems. This enables rapid system interaction, reduced manual operations and thereby lead-times.</p>	<ul style="list-style-type: none"> ▪ Lead-times ▪ Gathered Batch Documentation ▪ Documentation Deviations 	<ul style="list-style-type: none"> ▪ System Deviations ▪ Implementation Costs
<p>Audit Trail The operator's actions are recorded and stored in a database.</p>	<ul style="list-style-type: none"> ▪ Traceability 	<ul style="list-style-type: none"> ▪ Data Record Costs

Manufacturing Deviations

Deviations caused by the operator due to incorrect use of routines and manufacturing rules will be minimised by the workflow manager. The system will guide and assist the operator through important procedures, which facilitates a correct adoption of routines and manufacturing rules. Since the system to some extent is capable of controlling the outcome of the final product in real-time it would be preferable to adopt a proactive work culture, focused on handling problems before rather than after they occur. In other words, if the system detects that a manufacturing deviation is likely to occur it should notify the operator who makes necessary production adjustments that could save the entire batch.

Documentation Deviations

The EBR system will assist in the batch documentation process, which ensures that the documentation is complete and correct. A vast range of different types of documentation deviations will be reduced e.g. missed signatures, incorrect calculations, missing batch documentation and incorrect batch documentation. Documentation deviations can cause significant delays in production and increased costs of labour and WIP.

Scrap Costs

Different deviations may have different impact on costs. The most serious kind of deviations sometimes causes scrap of material, which can be very costly. Since the EBR solution can eliminate some deviations it is also very likely that scrap costs will be reduced as well. For instance deviations concerning incorrect use of routines and manufacturing rules are likely to cause scrap of material. Such deviations can be prevented by the use of procedural guidance.

Documentation Labour

Documenting a batch is often labour intensive. For instance, the operator needs to perform manual calculations, sign specific procedures, document certain process values and document used equipment. When the production is completed the documentation is manually screened and scanned for errors, calculations are verified and signatures checked. Sometimes tasks such as process value trending and communicating with other systems are additionally performed. A full EBR system will keep the costs for completing, screening and controlling batch documentation at a minimum, substantially reducing costs of labour and administration.

The fact that the screening and controlling process usually is performed by three or in some cases four instances per batch further enhance the positive impact of an automated system carrying out the task.

Automated Process Quality Control

After the production process is finished it is analysed by the quality department. The detection of process deviations may be facilitated by the EBR software, which in combination with manufacturing rules can highlight problem areas. This could make the deviation handling more effective and less time consuming. It is also possible to integrate the EBR system with QIMS but this is not investigated due to project constraints.

Traceability

In pharmaceutical manufacturing a high level of traceability is required to meet regulations. The EBR system enables a very high level of traceability by recording information intended for the batch protocol, process values and equipment usage. The storage of process values and equipment usage also enables a more effective management and scheduling of equipment.

Lead-time

There are different lead-times that are affected by an EBR system. Lead-times in the actual manufacturing process are unlikely to be directly reduced by the EBR solution. However, it is possible that new data from the EBR system can assist in the work with continuous improvements to make the manufacturing more effective. Routines can be optimised and new work procedures adopted due to the increased analysis capabilities.

The lead-times affected the most by an EBR system concerns quality control operations. Fewer deviations naturally imply shorter quality control lead-times. Additionally, the manual labour of controlling and reassuring correct status of batch documentation will most likely be dramatically cut. Besides cutting the man-hours of screening and controlling batch documentation, administration lead-times are also reduced to a minimum.

The EBR system allows quality control personnel to be directly faced with the manufacturing deviation, which enables them to address the problem immediately. This would certainly simplify the quality control work and, hence, decrease the quality control lead-time even more. It is also possible to integrate the EBR system with QIMS and thereby reduce the lead-times for even further.

Gathered Batch Documentation

When systems are integrated, the batch documentation becomes dynamic and all batch documentation can be accessed and presented in a desired way. The overall quality work becomes more efficient with a dynamic end batch document that contains signatures, quantities, process values, alarms, comments and complete audit trail. The quality personnel have access to all batch specific information in a single document, which enables them to work more effectively.

Storage Costs

Regulations enforces that batch documentation is stored for several years. However, the corresponding documentation for each batch is very large and the number of batches produced at the Gärtuna site is enormous. This results in a need of great storage capacity in order to comply with the regulations. Batch documentation is currently stored in large and safety demanding facilities. The facilities are rather expensive due to their size and their need to withstand fire and in other ways protect the batch documentation they hold. Hence, an EBR system facilitates the batch documentation storage and lowers the storage costs.

Batch documentation analysis is difficult and sometimes it requires substantial administrative efforts in order to obtain the correct documentation. Storing batch documentation electronically can solve these problems since the batch data is easily accessed for processing and review.

Data Record Costs

The introduction of a new data record inevitably brings many new costs. The least expensive cost is the server and the storage hardware. Obviously data records also need backup systems and safety functions such as access control. These are regulated in detail by 21 CFR Part 11. Many data records require a dedicated administrator, which usually is very costly. However, in comparison to traditional storage costs, the total costs for data records should be low.

Data Accessibility

When using a large data system there is always a risk of malfunction, which can cause inaccessibility of important manufacturing functions. This aspect is commonly handled by backup systems giving access to stored and cached manufacturing information. Other solutions incorporate the ability to switch between electronic and paper based instructions and documentation.

Complex Routine Procedures

Routines, SOPs and other manufacturing procedures are currently stored in a central database. Parts of this database need to be accessible to the procedural guidance function in the workflow manager. The operator should be able to easily view and consult routines and production rules during manufacturing. The workflow manager also incorporates program code that uses routine guidelines for controlling the adoption of standard procedures in manufacturing. When a routine is updated, the program code also needs to be updated. This will put high demands on the routine update and documentation process.

Inflexible Production

The workflow manager makes production less flexible since the operator must fulfil all routine requirements before advancing to the next step. This could imply a less effective scheduling of resources, cause various difficulties in production and increase lead-times. It is therefore important to carefully study actual manufacturing procedures in production and adapt current manufacturing rules and procedures so that they match.

5.2.4 MES Mapping

In Figure 21 the suggested EBR solution is mapped to the current AstraZeneca TPS model for MES and EBR earlier displayed in Figure 16. This gives a comprehensive map of current and new systems included in the suggested EBR solution for the Gärtuna site. It shows which current systems should be replaced by substitute systems and where additional functionality is needed. MFO and the EBR components in the developed solution are coloured grey and covers the systems they replace.

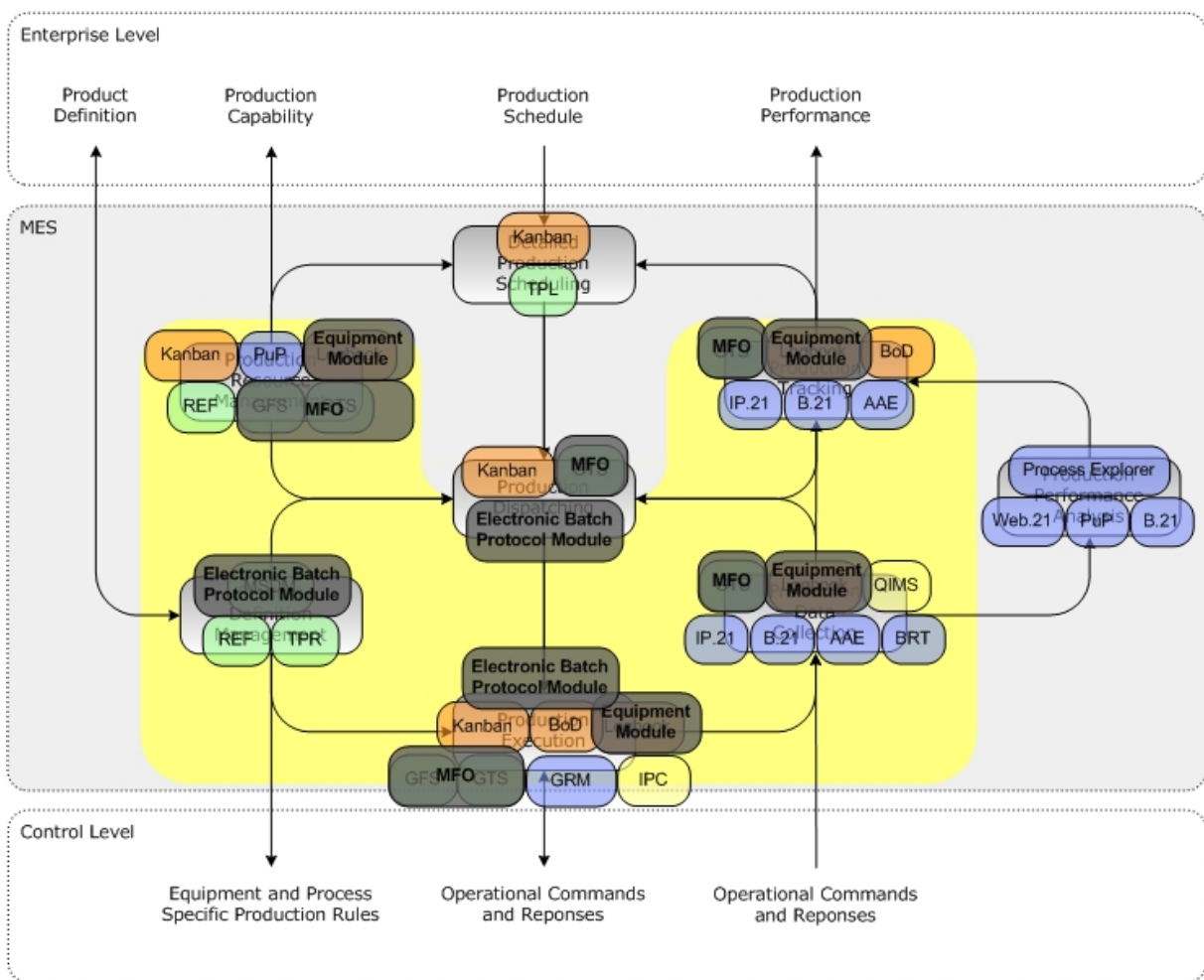


Figure 21: Mapping of the developed EBR solution to the MES model established by ISA 95

The Electronic Batch Protocol Module constitutes a considerable part of the system and involves both *Production Dispatching* and *Production Execution Management*. Additionally, it includes much of the MSDM functionality such as SOPs, routines and other manufacturing instructions. Hence, there is a substantial EBR focus on the *Product Definition* activity.

The EBR system replaces the manual logbook with the Equipment Module. This database management system is an important part of the EBR system and affects many activities in the MES model.

The MFO system will replace GTS and parts of the warehouse system GFS. Thus, the MFO system will comprise a major part of the EBR system and be involved in several functional activities.

5.3 CONCLUSION

In order to get a comprehensive picture of the current systems involved in manufacturing operations, a detailed information flow analysis was undertaken. Relevant systems influencing the batch documentation, manufacturing procedures and workflow were mapped and analysed. Together with project constraints and ongoing system developments the identified current systems enabled the establishment of the primary EBR system functionality required at AstraZeneca TPS.

The Equipment Module, which replaces the current logbook, constitutes a significant part of the EBR solution. Another substantial part concerns the introduction of workflow management functionality, which is included in the Electronic Batch Protocol Module. The last considerable component in the solution is the MFO system, which is currently under development.

The complete EBR solution is compliant with the ISA 95 model for MES as far as EBR functionality is concerned. From a MES perspective AstraZeneca TPS would include most of the ISA 95 activities in the production view. However, the AstraZeneca TPS MES model includes very little scheduling functionality and should preferably be complemented with additional production process analysis functionality.

There are many advantages but also some disadvantages with the introduction of an EBR system. Hence, it is imperative to evaluate the benefits and the detriments with the system after its implementation. Consequently, some relevant metrics have been established that would enable a quantitative measure of the system performance prior and subsequent to an EBR introduction. These metrics are displayed in Table 11.

Table 11: Metrics for quantifying the EBR systems performance

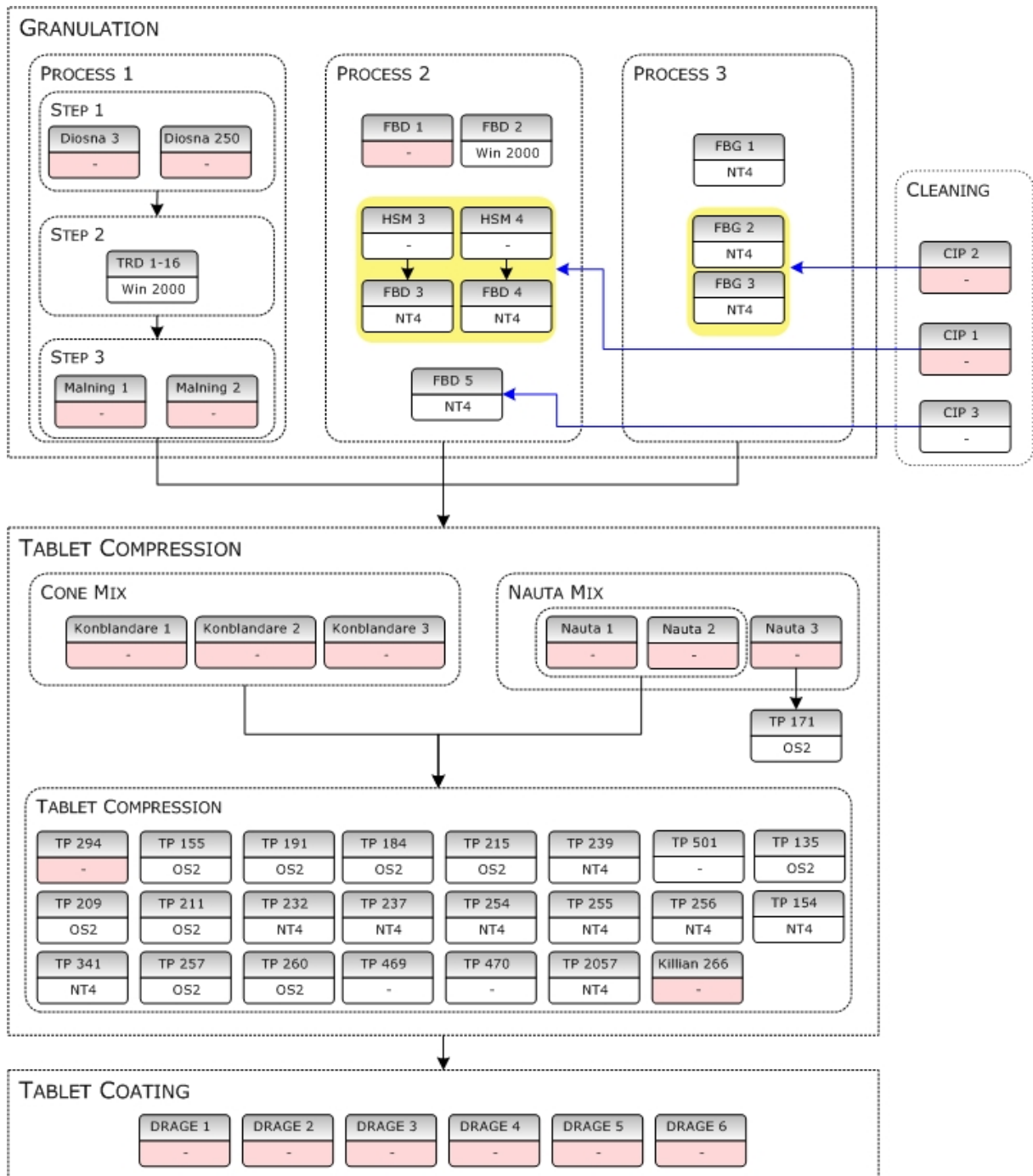
Performance Metric	Analysis
Number of Deviations	Initially the EBR system might yield an increased number of overall deviations. Whilst the number of manual and documentation deviations should be decremented a natural increase in system related deviations is anticipated. Thus, when the initial running problems are solved a significant proportion of the overall deviations should be eliminated by an EBR introduction.
Scrap Value	A decrease in the number of deviations would most certainly lower the production related scrap value. The yearly scrap value is significant but it is very difficult to classify its specific causes. However, analysis of scrap classified as <i>manual</i> or <i>expired date</i> should be lowered with an EBR introduction.
Production Lead-time	An EBR introduction may not affect the production lead-time. Some operations will be superfluous and the elimination of those should cut the production lead-time. On the other hand the procedural guidance function will make the order of operations stricter and might therefore increase the production lead-time. Initially after an EBR system introduction the lead-time will most certainly increase but in a long perspective it should be lowered.
Quality Control Lead-time	An EBR system should eliminate most of the work performed by operator controllers and sincerely simplify the quality control work. Hence, an EBR introduction should significantly make this work more effective yielding lower quality control lead-times and a reduction in WIP costs. Most likely the decrease in quality control lead-time renders the greatest impact on overall lead-time.
Documentation Quantity	An EBR system introduction should lower the number of manual documentation operations and hence the number of signatures. Less manual operations releases work force and lowers the risk of introducing deviations. A comparison of the number of signatures before and after an EBR introduction quantifies the degree of simplifications done to the operator working tasks.
Batch Documentation Storage	With an existing EBR system the storage cost would mainly concern data hardware, software and support costs split by a large number of batches. A calculation of the storage cost per batch before and after an EBR introduction enables a quantification of the possible cost reduction regarding batch documentation storage. These costs are expected to decrease with an EBR introduction.
Production Labour	An EBR system implies that the operative staff, particularly concerning operator control, carries out fewer procedures. Hence, the risk of having excess staff is apparent. A comparison of the size of the labour force before and after an EBR introduction reveals whether the production is becoming more effective or not. The production is anticipated to become more efficient since the same tablet quantities should be produced by a smaller labour force.
Quality Control Labour	An EBR system including quality control functionality should sincerely simplify the quality control work. Hence, the quality control labour force will face an apparent risk of having excess staff. A comparison of the size of the labour force before and after an EBR introduction should reveal how much more effective the production and the quality control function has become. Fewer deviations imply less quality control work and a more efficient quality control work decreases the need for quality control labour.
Support Labour	With an EBR introduction it is obvious that the system support group needs to grow. The new data and information systems need support and maintenance staff to secure reliability and prevent system failure. The corresponding costs are directly linked to the EBR system and yield a measure of its success regarding architecture and implementation.

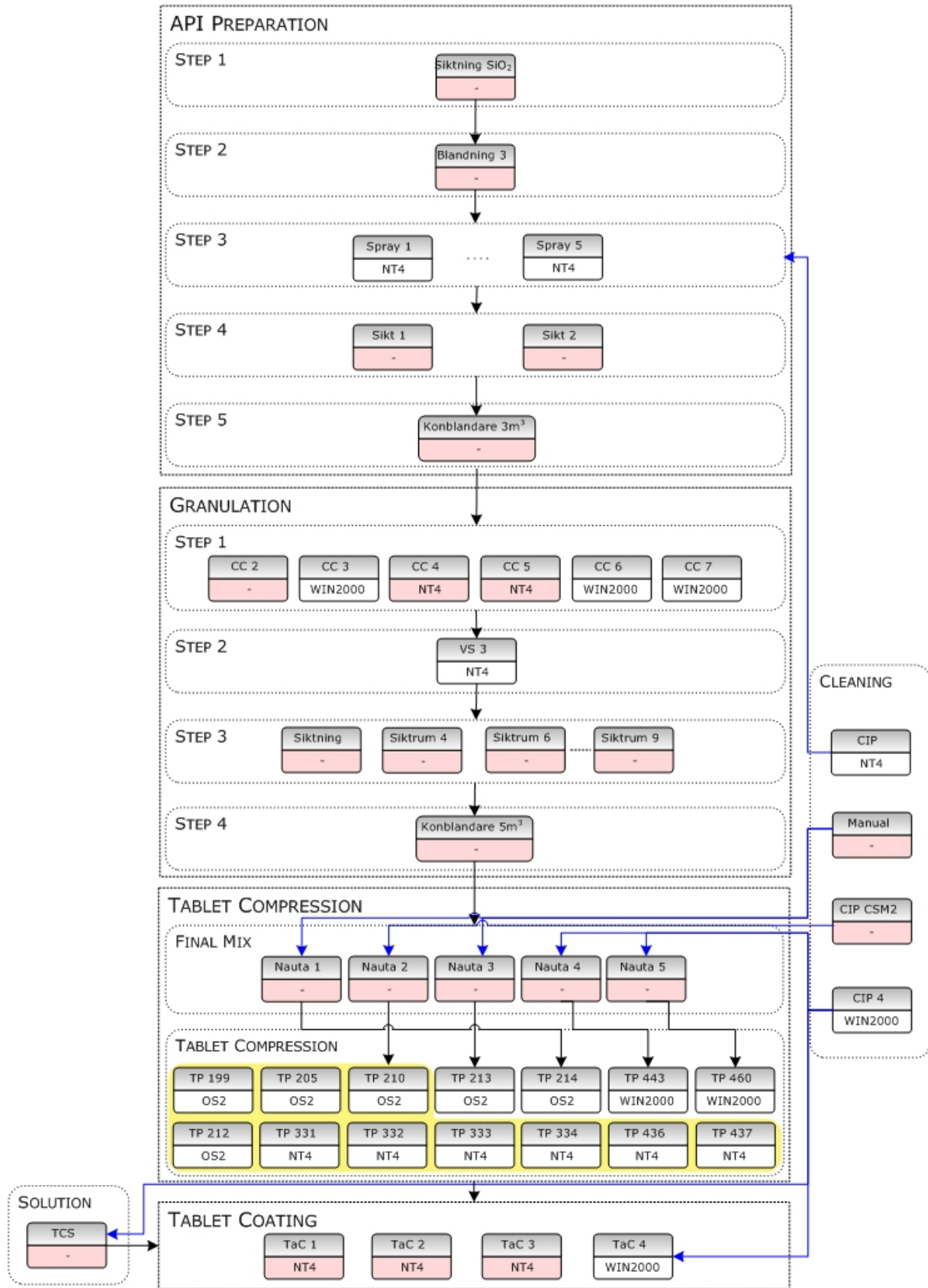
6.0 Appendix A

The mapping of all candidate production areas at AstraZeneca TPS is displayed in the section below. The main material flow between manufacturing equipment is covered. However, material flow to and from warehouse and transitory storage rooms is not included in the mapping. For confidentiality reasons some minor information is left out of the maps. An explanation of the mapping is given in the following paragraph.

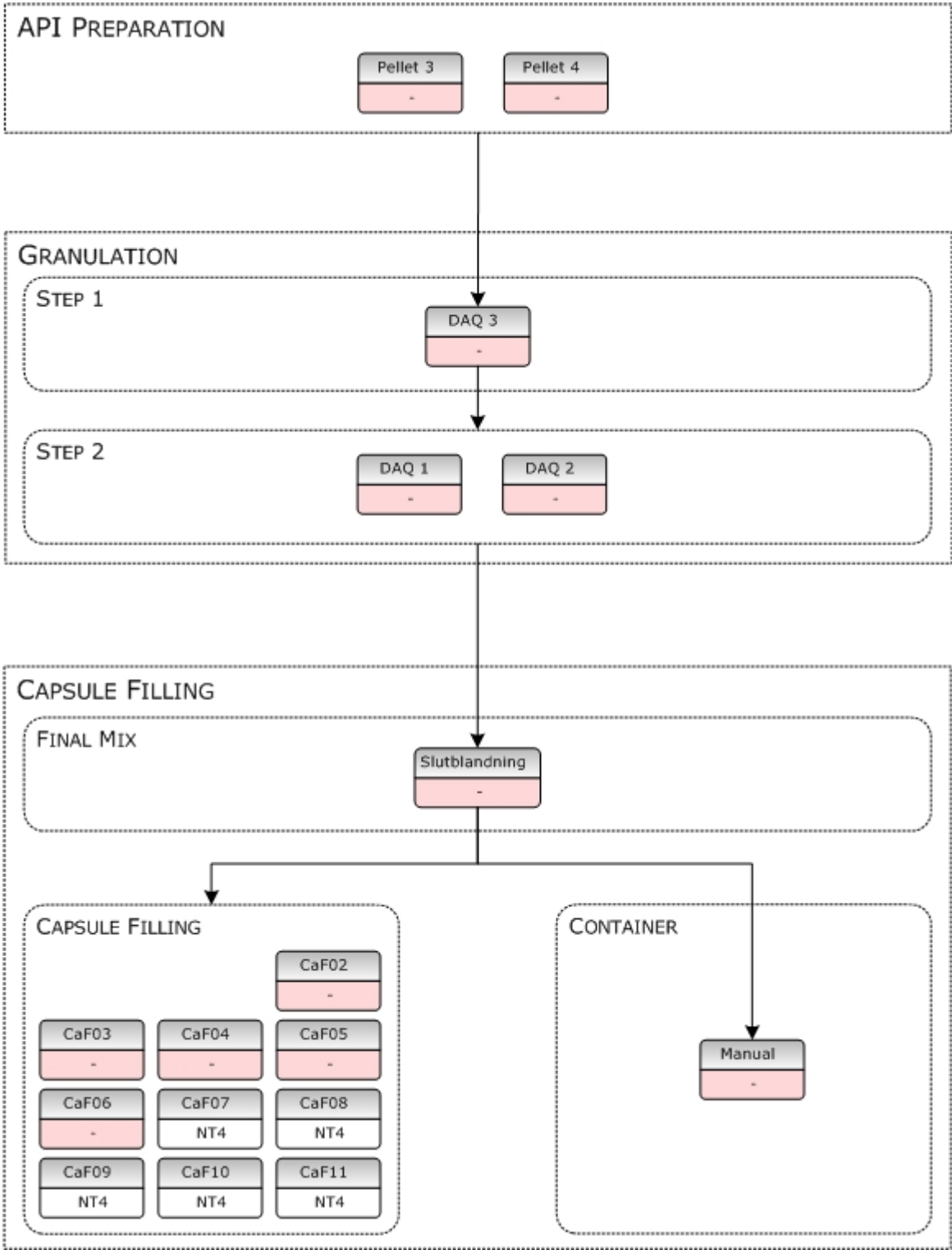
- Each box in the maps equals a specific equipment entity.
- Each box has two text fields, one shaded on top containing the equipment name and the other below containing the operating system to the belonging SCADA, where applicable.
- Equipment being connected to PIST has a pink coloured box bottom.
- Equipment being dedicated to each other is joined in a blue group.
- Groups of equipment being provided by common supplier equipment or supplying to single equipment are joined in a yellow group or circled by a dotted line.
- Black arrows mark material flow between equipment.
- Red arrows mark material flow to and from control operations.
- Blue arrows mark workflow provided by sanitation equipment or personnel.

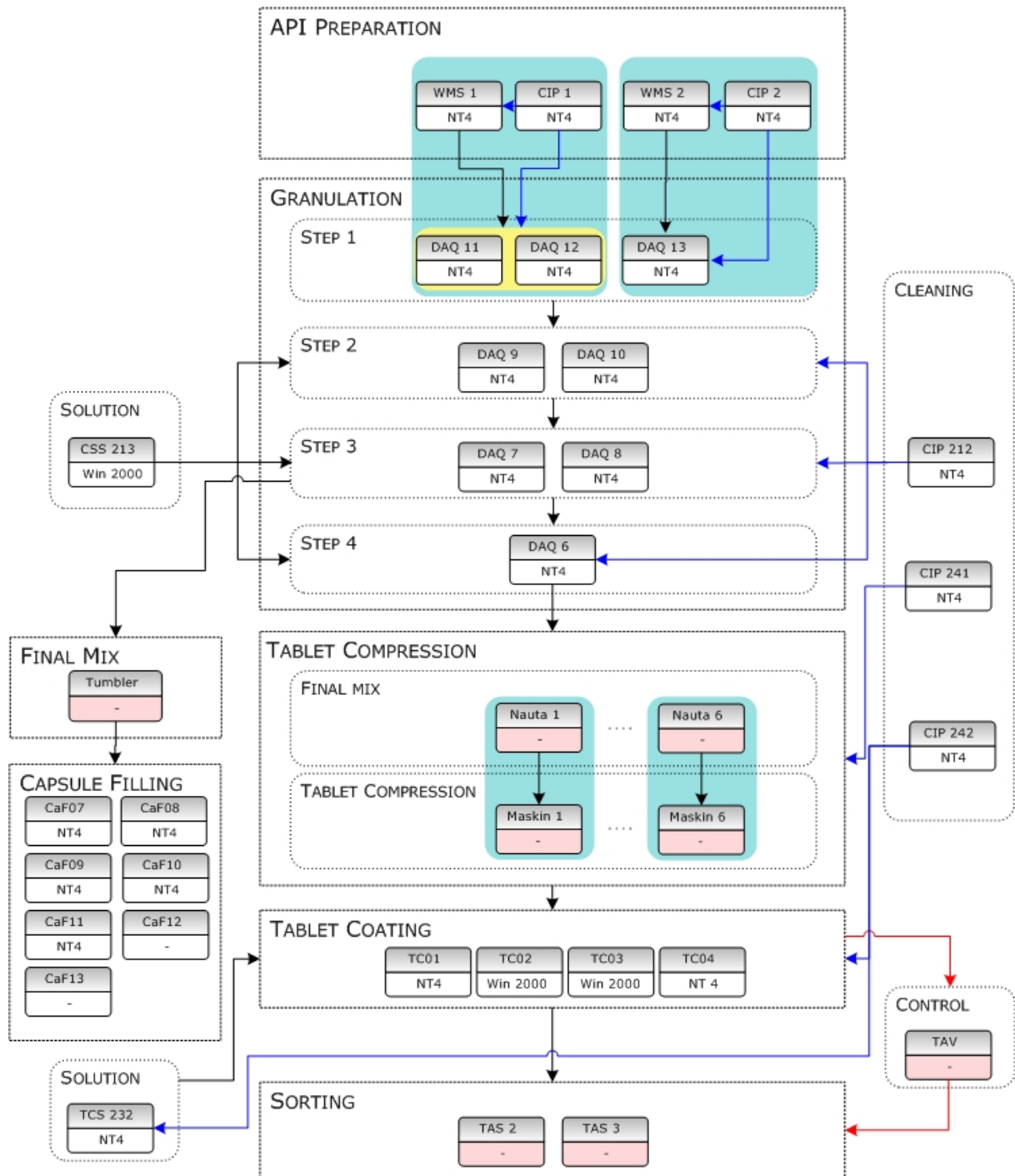
611 TPT

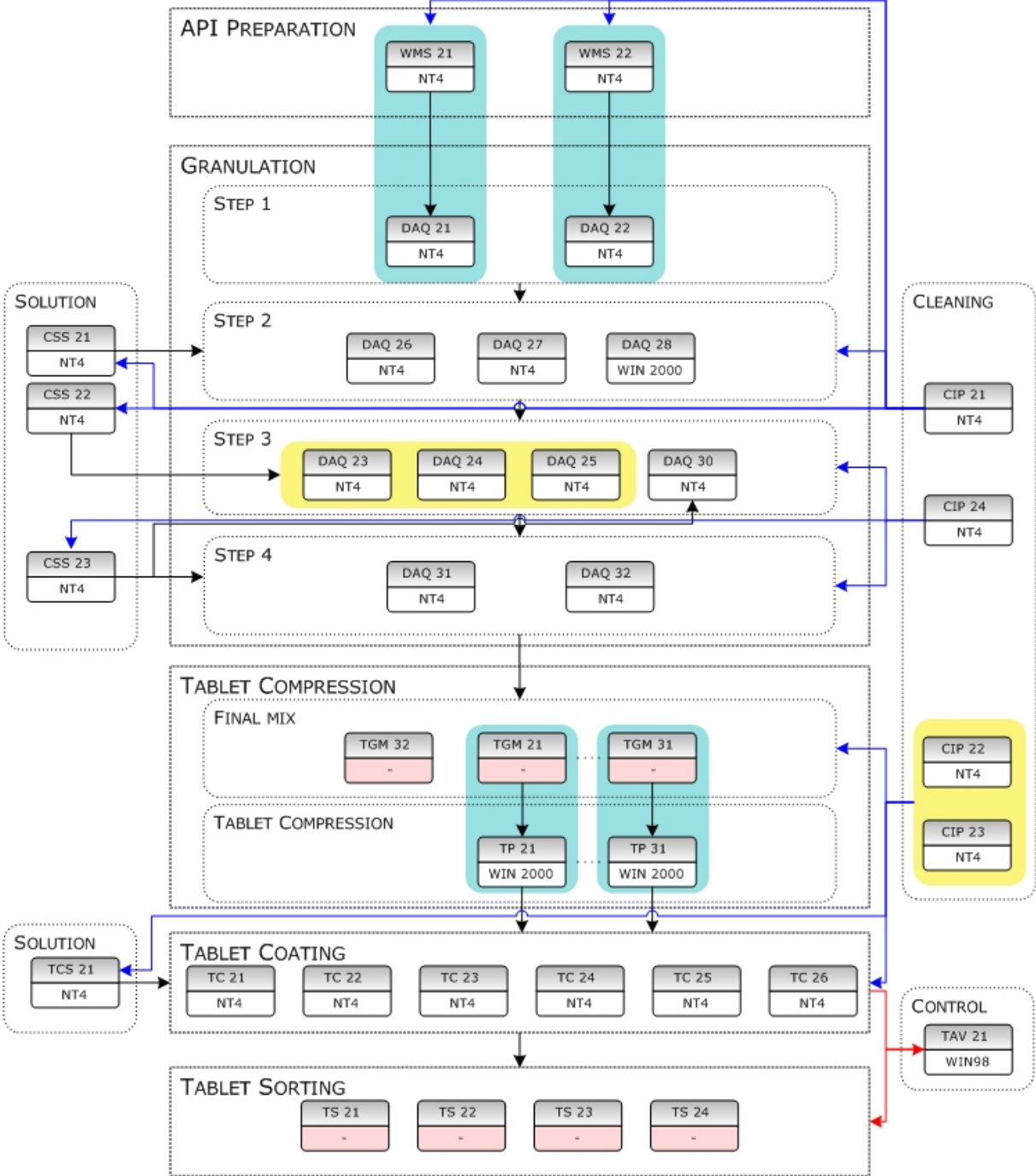




614 TPD







7.0 Appendix B

The aim of this appendix is to explain the function of an EBR during manufacturing at Gärtuna for the selected production area. Accordingly, the EBR manufacturing scenario is valid for the FBD processes for Candidate E. Relevant process steps and procedures are discussed and explained in sequential order under the subtopics below.

Manufacturing Order Initiation

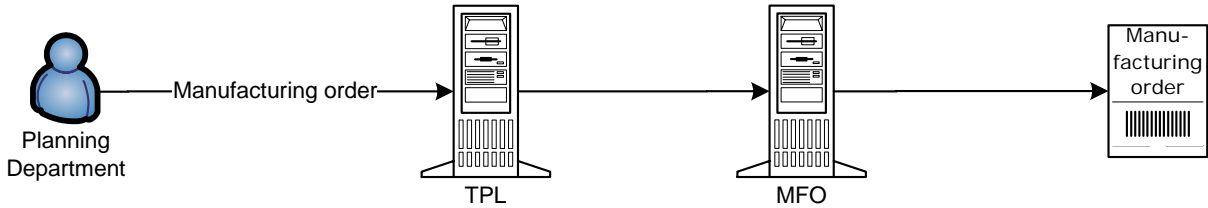


Figure 22: Initiation of a manufacturing order

Before being able to manufacture, the operator will require a manufacturing order. This is given to them by the Planning Department through MFO. The Planning department uses various systems to schedule and manage production. However, TPL is the central planning system and is the initiator of the manufacturing order. After the manufacturing order has been issued in TPL, it is forwarded to the manufacturing system MFO. The process is shown in Figure 22 .

Manufacturing staff uses the MFO system to receive the scheduled manufacturing order. It is printed in order to physically represent itself on the Kanban queue rack, which is currently used at Gärtuna.

Label Print

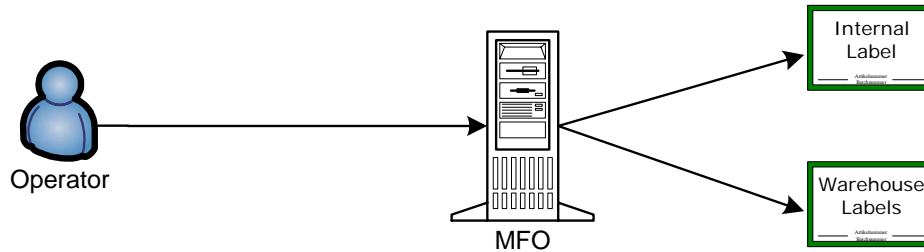


Figure 23: Label printing from the MFO

Before manufacturing is started, manufacturing staff use MFO to print internal labels for equipment, laboratory tests and outgoing material destined to other process cells belonging to the same production area. The MFO system additionally prints labels for outgoing material to the warehouse but this is performed after the batch has been manufactured. The process is shown in Figure 23.

The internal labels contain information about the product being manufactured, such as article number and batch number. A major difference from current internal labels is that the batch number is automatically registered on the label. The label also carries a field for attaching a barcode, which is after manufacturing connected to information regarding weights and other metrics stored in the MFO system.

Start of the Electronic Batch Protocol Module's workflow manager

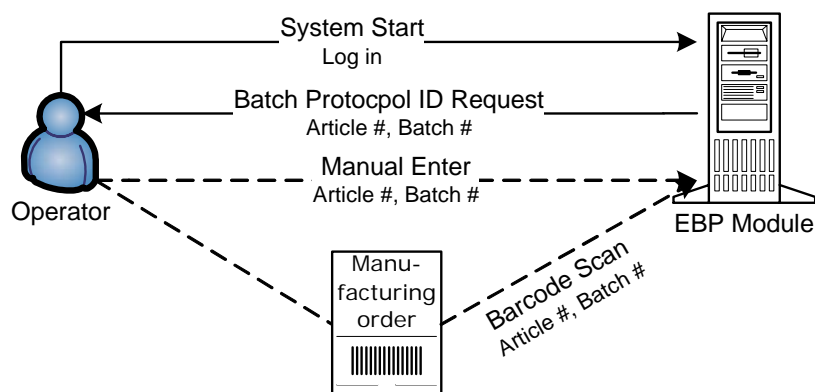


Figure 24: Start of the Electronic Batch Protocol Module's workflow manager

When an article is scheduled for manufacturing and incoming materials are present, the operator can start the workflow manager in the Electronic Batch Protocol Module.

The operator logs on to the EBP module and is requested to select a batch protocol workflow. In order to select the correct batch protocol from the BPTD and the correct information from the BPCD, the EBP module needs a unique batch protocol id from the user. In this case it is suitable to use the article number and batch number as a primary key which is therefore requested from the operator.

There are different ways for the user to communicate the batch protocol id to the EBP module. A preferable way of doing this is to scan the barcode on the manufacturing order, but it should always be possible to enter the information manually into the EBP system. The EBP system creates a new instance of the selected batch protocol in the BPCD. If the id has been registered before, the saved batch protocol workflow is opened and started from the correct position. The process is shown in Figure 24.

Materials Arrival Control

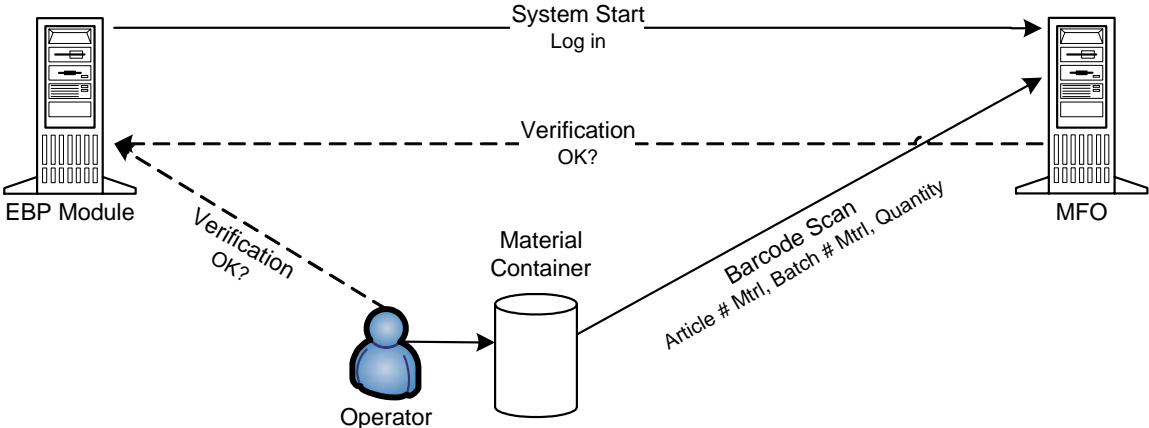


Figure 25: Scenario 1, Barcode scanning managed by the MFO System

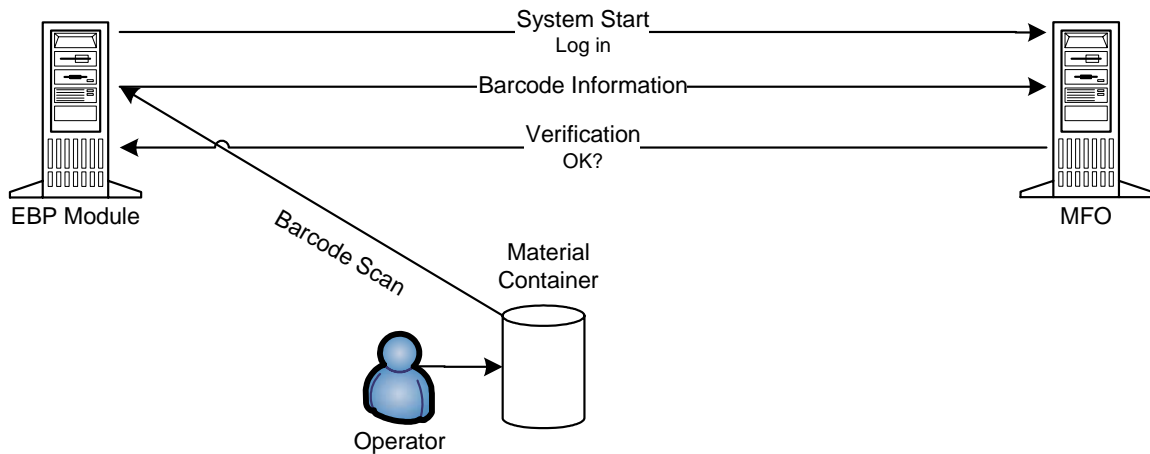


Figure 26: Scenario 2, Barcode scanning managed by the EBP module

The materials arrival control is currently not a mandatory procedure; however, many production areas apply it to ensure that no material is missing when production starts. In some production areas the entire batch might be scrapped if material is missing even for a relatively short period of time.

The workflow manager in the EBP module preferably initiates the materials arrival control by launching MFO or accessing its databases. If MFO is launched, the user is either automatically or manually logged in to the system.

Depending on the desired system functionality and intersystem communication complexity two scenarios for a possible solution has been established. The first scenario, shown in Figure 25, is based on the current MFO solution in which the MFO system performs the entire material control function. The operator scans the material id in to the MFO system, which then controls article number, batch number and quantity of the received material according to specifications in the manufacturing order that is stored in the system. The operator will receive a confirmation by the MFO user interface whether or not the material agrees with the specifications on the manufacturing order. The result from the MFO control will be communicated to the EBP either manually by the operator or automatically by the MFO system.

The second scenario, shown in Figure 26, is similar to the first but the materials arrival control is performed via the work flow manager in the EBP module. The workflow manager in the EBP requests the user to scan information from the barcode label attached to the

incoming material. This way the scanning functionality is centralised to the EBP system, which preferably also has such functionality in order to effectively communicate barcode information with the Equipment Module. The materials information scanned to the EBP system is forwarded to MFO, which performs the same evaluation as in the first scenario. A verification signal is thereafter sent to the EBP system, which is presented to the operator through the graphical user interface.

Start Report

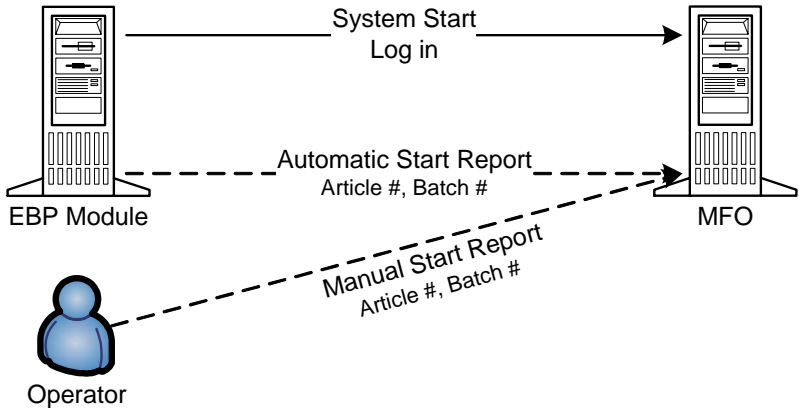


Figure 27: Scenario for start report

Before the actual production begins a start report must be given to the MFO system, which then communicates relevant information back to the TPL system.

The start report could preferably be done automatically by the EBP application when the batch protocol is created, triggered by a signature from the operator. However, it should also be possible to perform the start report manually by the operator shown in Figure 27.

Equipment Registration

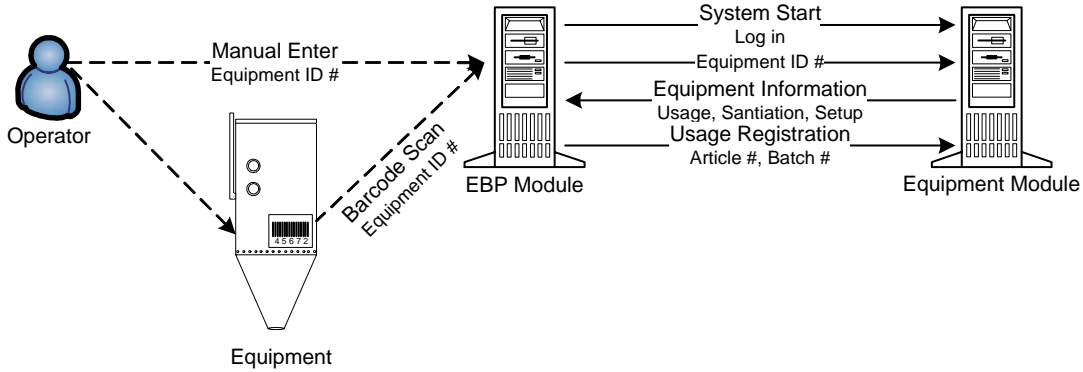


Figure 28: Equipment registration scenario

All equipment used during manufacturing must be registered for traceability reasons. The EBP module starts of by logging on to the Equipment Module automatically. However, the operator could manually log on to the system if necessary. The workflow manager in the EBP module initiates equipment registration by the manufacturing staff. The equipment id number must thereafter be given to the Equipment Module. The equipment id is preferably scanned from a barcode that is physically located on or in the vicinity of the manufacturing equipment. However, it should also be possible to manually enter the equipment id number.

The EBP communicates the equipment id number to the Equipment Module, which returns equipment specific information concerning use, sanitation and setup. The information is validated by the workflow manager in the EBP module and is also compared to specifications from the BPTD. If the system accepts the status of the manufacturing equipment, the EBP module will send the article number, batch number, operator id and start time to the Equipment Module for storage. In case the equipment status violates the manufacturing rules, the operator will be guided through the correct procedures and routines for adjusting the problem. The process is shown in Figure 28.

Materials Mixture Control

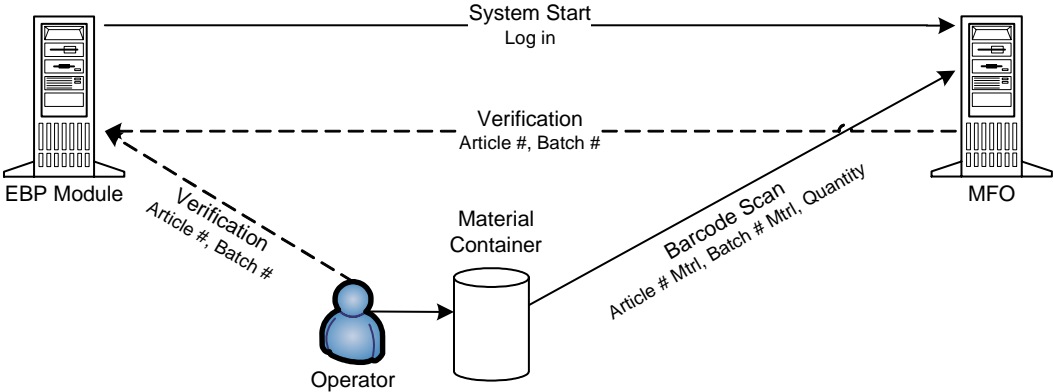


Figure 29: Scenario 1, Barcode scanning managed by the MFO System

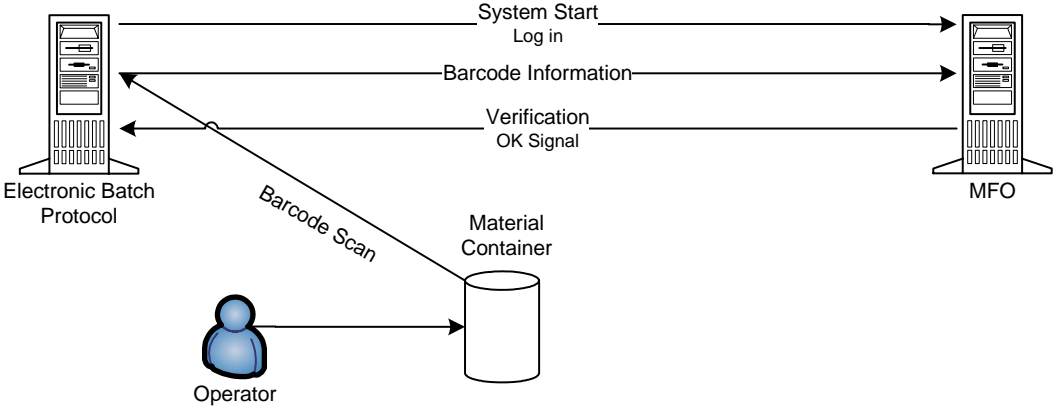


Figure 30: Scenario 2, Barcode scanning managed by the EBP module

It is necessary to control and document the id and quantity of incoming material when adding it to the manufacturing process. It is therefore suitable to place materials control functionality in the workflow manager. The procedure and complexity of the function is very similar to the materials arrival control.

Depending on the desired system functionality and intersystem communication complexity we have established two scenarios for a possible solution. The first scenario is based on the current MFO solution in which the MFO system performs the entire materials mixture control function. The operator scans the material barcode in to the MFO system, which then controls article number, batch number and quantity of the material according to specifications in the manufacturing order that is stored in the system. The operator will receive a confirmation by

the MFO user interface whether or not the material agrees with the specifications on the manufacturing order. The result from the MFO control will be communicated to the EBP either manually by the operator or automatically by the MFO system. The process is shown in Figure 29 .

The second scenario is similar to the first but the materials mixture control is performed via the workflow manager in the EBP module. The workflow manager requests the user to scan information from the barcode label attached to the incoming material. This way the scanning functionality is centralised to the EBP system. The materials information scanned to the EBP system is forwarded to MFO, which performs the same evaluation as in the first scenario. A verification signal is thereafter sent to the EBP system, which is presented to the operator through the graphical user interface. The process is shown in Figure 30.

Solution Selection and Recipe Selection, Scenario 1

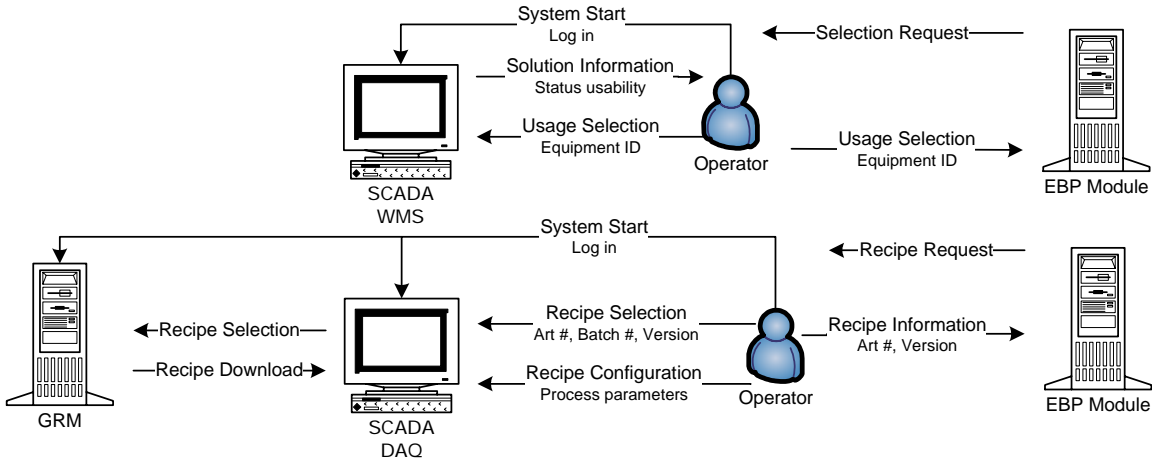


Figure 31: Selection of recipe and solution to the FBD process unassisted by the EBP module

There are two steps that must be made before executing the manufacturing of a batch on a FBD. A solution has to be selected and a recipe has to be chosen. There are two possible choices of SCADA interaction when selecting the solution and recipe for the manufacturing process, either not involving the EBP module at all or putting the EBP module as a supporting application. This will describe the first scenario where procedures are handled manually by the user and thereafter stored in the EBP module, which is shown in Figure 31.

The workflow manager requests the operator to select a solution. The operator logs in to the SCADA and receives important parameters about the solution. The solution parameters are studied and the optimal solution is chosen and reported to the SCADA. The operator thereafter documents the selection of solution in the EBP module manually.

The operator logs on to the SCADA and the GRM system. The EBP application thereafter requests the operator to select a recipe for manufacturing. The operator studies the recipe parameters and chooses the correct recipe for the process, which is then downloaded to the SCADA. The operator thereafter documents the selection of recipe in the EBP module manually. Any recipe configuration is made manually by the operator and is then documented in the EBP module.

Solution Selection and Recipe Selection, Scenario 2

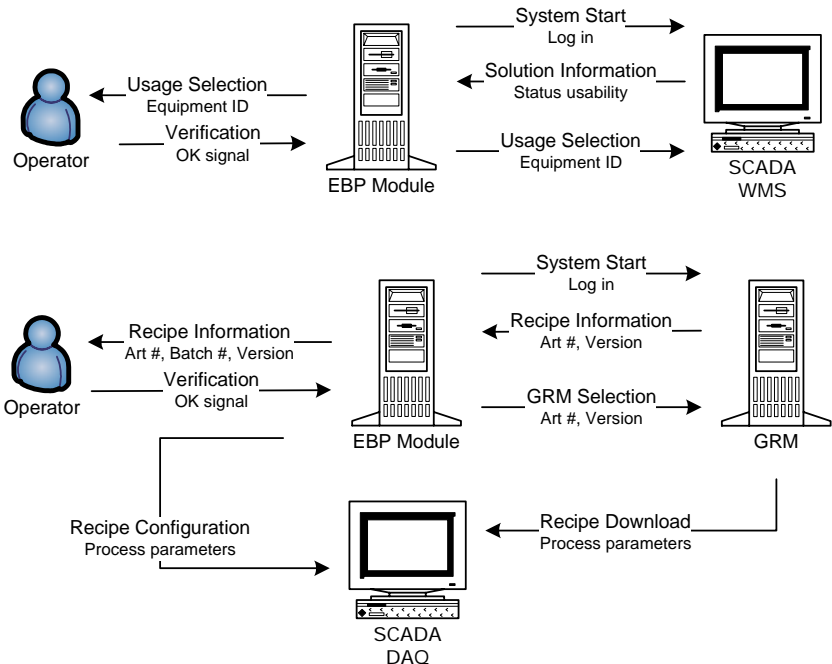


Figure 32: Selection of recipe and solution to the FBD process assisted by the EBP module

The scenario for selecting the solution and recipe assisted by the EBP module is shown in Figure 32 and described below.

The EBP logs on to the SCADA and retrieves important data about available solutions. The solution parameters are studied and the optimal solution is chosen automatically. The EBP workflow manager requests the user to confirm if the chosen solution is correct. If the user agrees a verification signal is transmitted to the EBP module, possibly using signatures. After the verification signal has arrived, the selection of solution will be notified to the SCADA.

The EBP logs on to the GRM system and retrieves information about the recipes for the desired article. The recipe parameters are analysed and the correct recipe for the process is chosen. The EBP workflow manager gives the recipe information to the user, if the user agrees with the choice of recipe a verification signal will be transmitted to the EBP module, perhaps using signatures. The recipe is thereafter downloaded to the SCADA by the EBP module and any necessary configuration of the recipe is performed automatically. The operator confirms any necessary configuration with a verification signal.

Process Run, Scenario 1

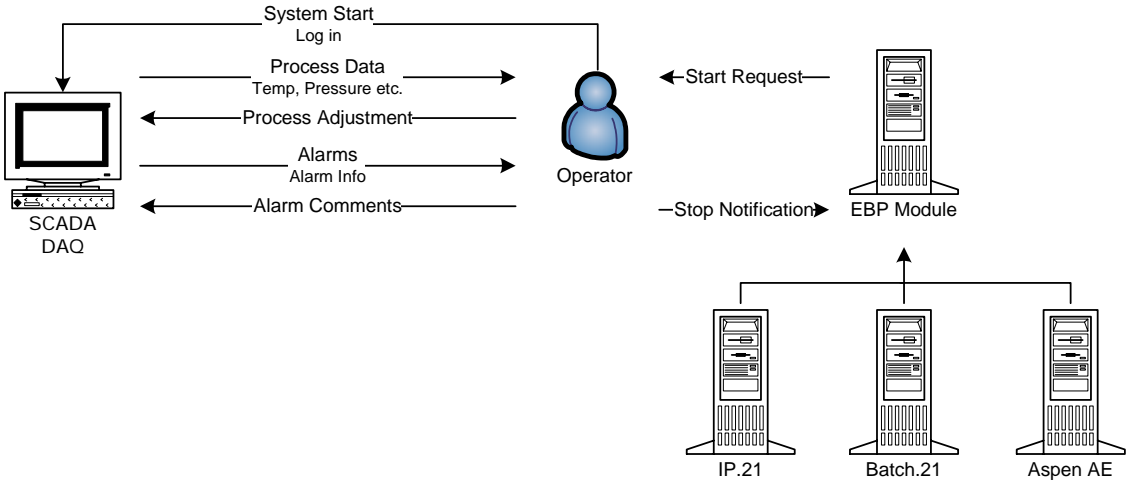


Figure 33: FBD process run without EBP module

As with the solution selection and the recipe selection processes there are two core scenarios that can be used during manufacturing. Using the SCADA software as a separate, independent application or putting the EBP as a shell interface over the SCADA software handling the user communication. The first scenario is shown in Figure 33 and described below.

The EBP workflow manager requests the operator to start the production process. The operator thereafter logs on to the SCADA and initiates manufacturing. Process data is available from the SCADA and the operator analyses relevant graphs and measurements. Alarms are also presented and can be commented by the operator. The comments are stored in a modified Aspen AE database.

The Operator can make process adjustments by using the SCADA software. After manufacturing the batch, the documentation is completed with relevant tags from the IP.21 database, batch data from the Batch.21 database and alarms from the Aspen AE database.

Process Run, Scenario 1

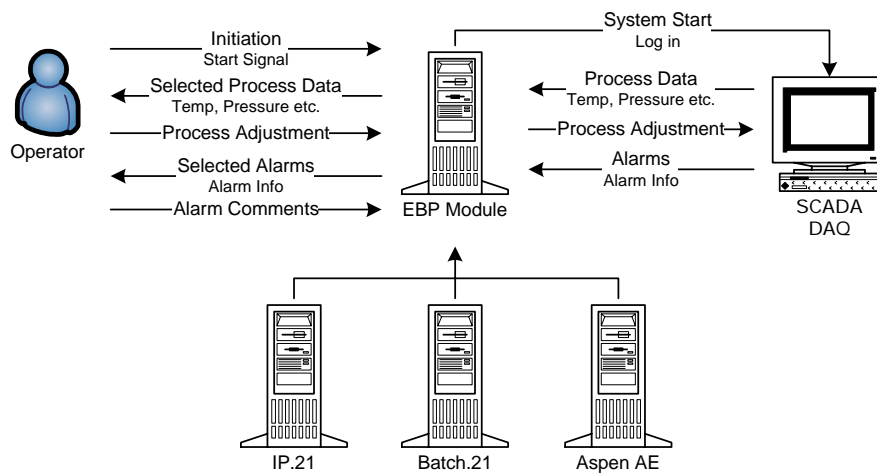


Figure 34: FBD process run with EBP module

The second scenario for a process run, which highly involves the EBP module, is shown in Figure 34 and described below.

The workflow manager in the EBP module logs on to the SCADA and requests the operator to initiate manufacturing. The operator transmits the start signal to the EBP, perhaps using signatures. The EBP module then starts the manufacturing process through the SCADA. Process data is available from the SCADA and the EBP workflow manager presents relevant graphs and measurements to the operator. Alarms are also presented and can be commented by the operator. The comments are stored in the EBP module or in a modified Aspen AE database. Process adjustments are made through the EBP module, which are then redirected to the SCADA control system. After manufacturing the batch, the documentation is completed

with relevant tags from the IP.21 database, batch data from the Batch.21 database and alarms from the Aspen AE database.

Equipment Usage Stop Registration

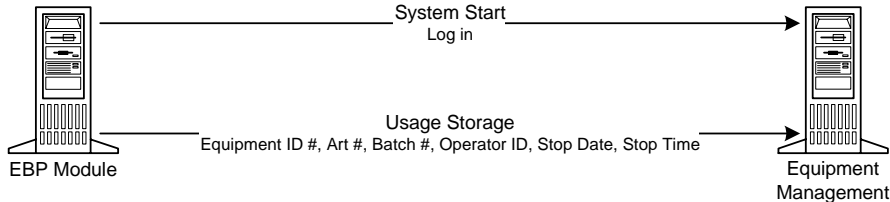


Figure 35: Storage of equipment usage data to Equipment Module

After the production of a batch is finished, the stop date and stop time is stored for all used equipment, which is shown in Figure 35. The EBP module does this automatically after the process run.

End Report

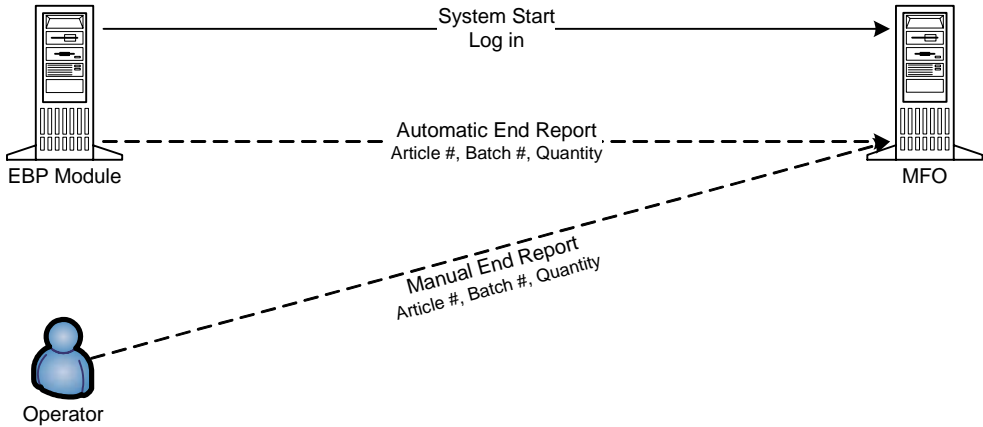


Figure 36: End report procedure

When the actual production is finished an end report must be made to the MFO system, which then communicates relevant information to the TPL system. The procedure is shown in Figure 36.

The end report is preferably made automatically by the EBP application after the batch manufacturing has stopped, perhaps triggered by a signature from the operator. However, it is also possible to perform the end report manually by the operator.

Each material container is also registered to its corresponding article number, batch number and quantity in MFO. After each container has been weighed, the quantities are stored in the system. Barcodes are printed and attached to certain designated fields on the internal labels. The barcodes are then linked to the container information in MFO so that they can serve as physical identifiers for the containers. If the material is leaving for the warehouse, a specific warehouse label is also printed from the MFO system. Each material container is registered one at a time or all at once in the MFO system, by having the operator selecting which container to register from a table displaying weighed leaving containers.

8.0 ACRONYMS

AEE – Aspen Alarm & Event

API – Active Pharmaceutical Ingredient

B.21 – Batch.21

BPCD – Batch Protocol Contents Database

BRT – Batch Report Tool

BPTD – Batch Protocol Template Database

CoGm – Cost of Goods manufactured

CR – Control-Release

EBP – Electronic Batch Protocol

EBR – Electronic Batch Record

ER – Electronic Record

ERP – Enterprise Resource Planning

ES – Electronic Signature

FBD – Fluid Bed Dryer

GRM – General Recipe Manager

GFS – Gärtuna Förrådssystem

GTS – Gärtuna Tillverkningsystem

IP.21 – InfoPlus.21

IPC – In Process Control

MFO – Manufacturing Operations

MES – Manufacturing Execution System

MSDM – Manufacturing Site Document Management

PIST – Process Information System Tablets

PuP – Produktionsuppföljning nyckeltal

QA – Quality Assurance

QIMS – Quality Information Management System

QT – Quality Technician

REF – Referensdatasystemet

SCADA – Supervisory Control and Data Acquisition

SOP – Standard Operating Procedure

TPL – Tablett Produktion Ledning

TPR – Tablett Processutveckling

TQ – Tablet Quality

WIP – Work In Progress

WIPV – Work In Progress Value

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