

2. State of the Art

In this chapter the theoretical background to the research problem is reviewed. The chapter is structured top-down, starting with the review of supply chain and operations management literature in general and ending with specific aspects of the batch record documentation process. The chapter firstly provides an overview about the relevant supply chain and operation management literature before then introducing evaluation models and data collection methods relevant for the research problem. The second section reviews literature about the pharmaceutical supply chain and introduces important aspects within the pharmaceutical supply network and between the manufacturing tiers that need to be considered in the research. The third part reviews relevant literature about the meaning and requirements of the batch record documentation process in the pharmaceutical manufacturing before then introducing the state-of-the-art in Electronic Batch Recording Systems, Manufacturing Execution Systems and the ISA-95 standard model.

2.1 Supply Chain and Operations Management

2.1.1 *Supply chain and operations management in general*

Definitions supply chain and operations management

Supply chain management is an omnipresent topic that can be found throughout current research and in real-life practice. The continuous growth of services, products, information and funds being distributed around the world makes this field of research one of the most exciting topics in research today. Although supply chain management has been very popular in research since the early 90th, there is only relative limited supply of validated models

outlining the scope, form, costs and benefits of supply chain management [CRG00].

Operations management is another field of research even though both disciplines, supply chain management and operations management, are closely linked together and interdependent.

Operations management embraces all activities of managing the resources and all processes that produce and deliver products and services [SL80]. In other words it is the transformation process that creates value by converting inputs (e.g., raw materials, labor, and information) into output (e.g., products, services) [STE12].

In the context of batch record documentation, both supply chain management and operations management are important. Batch record documentation occurs on all tiers of the pharmaceutical supply chain and within each operation. It can be seen is an integrated process within the pharmaceutical supply chain and within the operations; however with a stronger impact on the operations. Because of this, the literature review introduces both research areas but with a stronger focus on operations management and its performance objectives.

Originally, the term supply chain management described the potential benefit of integrating the internal functions of purchasing, manufacturing, storing and distribution into a set of coordinated activities [HAR96]. While every factory can run its manufacturing very efficiently, the organization as a whole may perform on a sub-optimal level. The terms ‘chain’ refers to the image of products or supply moving from one tier to the next tier along a chain. Christopher [CHR05] views supply chains as a whole, as a single entity, instead of a chain with different firms and fragmented responsibility.

In academic literature there are many definitions of the term supply chain and supply chain management available. For this examination, Chopra and

Meindl's [CM10] definition of supply chains as a **network consisting of suppliers, manufactures, transporters, warehouses, retailers and even customers** will be used; these are all parties involved in fulfilling a customer request.

Supply chain management is a series of activities that deal with planning, coordinating and controlling materials, parts and finished products from vendor to customer [STE89]. It includes the flow of material and the flow of information through the involved organizations. The key objectives of these activities, namely the objectives of supply chain management, can be summarized as the (i) maximization of profits and profitability [CM10], (ii) achievement of competitive advantages [STE89], (iii) increase in cooperation [CHR05], (iv) creation and the improvement of customer satisfaction [SHA04].

While supply chain management focuses externally on the entire network to provide the basic sources of input and to deliver the final outcome to the customer, operations management occurs internally within the organization [STE12]. **Figure 2** illustrates the supply networks from supplier to customer and the relationship between operations and supply chain management.

The supply chain is the network of firms from supplier to customer connecting the different operations. While company A's operations is part of the entire supply chain, a part of the supply chain is also part of company A's operations. So supply chain and operations couldn't exist without the other, and no enterprise could exist without both [STE12].

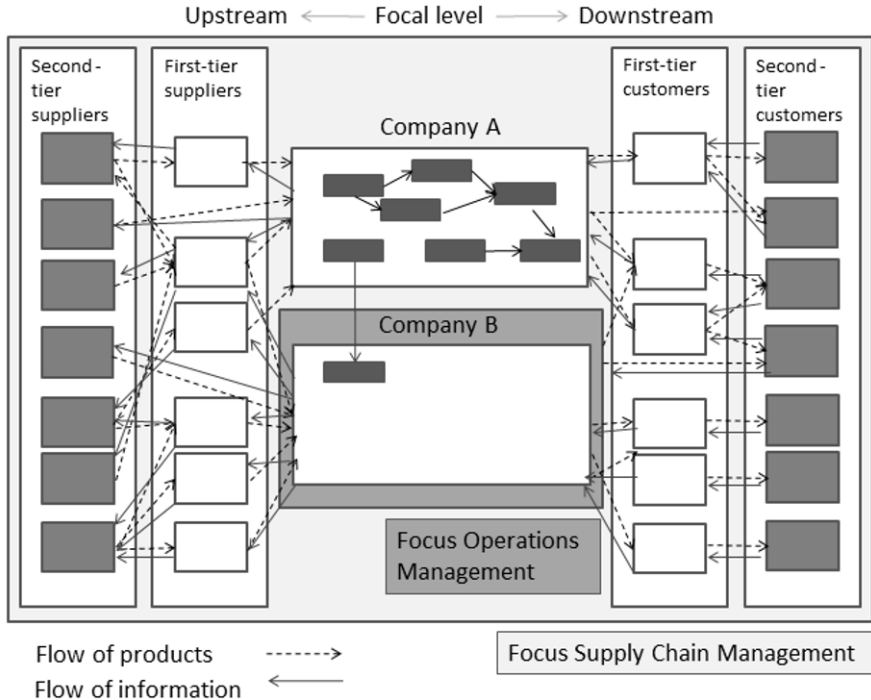


Figure 2, Supply networks are the connection between operations (ref. Slack and Lewis, [SL08], pg. 101)

The strategic view of operation management dates back to Skinner [SKI74]. In his view the operations (manufacturing) strategy derives from an overall competitive strategy; it should be understood and employed as a competitive weapon. The scope of operations management is much broader than just transformation. Today, main activities of operations management include [STE12; SL08]:

- system design and operating decisions related to product and service design,
- production of goods and service,
- capacity planning,
- process and location selection,
- work management,

- inventory and supply management,
- production planning,
- quality assurance,
- project management.

Objectives of operations management

The objective of any business requires an underlying rationale of the function, the very reason that the function exists [PY07]. As described in **Table 2**, there are multiple objectives discussed in regards to Operations Management in today's research. The most important ones are explained here.

Table 2, Operations management objectives

Objective	Source
Providing the supply or service capacity for expected demand	Stevenson [STE12]
Maximize operations performance in delivery speed, dependability, flexibility, costs, quality	Slack, Chambers and Johnston [SCJ04]; Slack and Lewis [SL08]
Increase competitive advantage through excellent performance	Slack and Lewis [SL08]
Creating and improving customer value through transformation and product/service delivery	Pycraft et al. [PY07]
Maximize the market criteria for success	Voss [VOS86]
Strategic strive for productivity through enhanced technology	Adam and Swamidass [AS89]

One objective of operations management is to ensure that the required supply and service capacity to meet the expected customer demand is available within the organization [STE12]. This means having adequately sized buildings and process technologies available in the right size, scale and number as well as possessing the right staff and other resources to be able to produce

goods based on customer needs [SL08]. A continuous reconfiguration in response to changed market requirements and customer demands is necessary to meet this goal.

Another objective is improving operations performance through the optimization of performance objectives. From an external (customer, market and authorities etc.) and internal (inside operations) perspective, quality, speed, dependability, flexibility and costs are the five important performance objectives [SL08; SCJ04; KLE07]. At this point these performance objectives and their impact to the operations will be described, albeit very briefly. In the next section, the performance objectives will be further discussed in the context of the pharmaceutical operations management and how these performance dimensions can be influenced through electronic batch recording technology.

Firstly, there is *quality*, since this is one of the most important performance objectives for authorities and based on the study of Readex Research [DA10] still the key focus within pharmaceutical operations due to the critical nature of product. Quality as performance objective refers to the specification of a product and how well a product fulfills this specification. Slack and Lewis (SL08) describe it as the fit for purpose. There are two aspects to this performance objective [SCJ04]:

First, providing good quality products to customers directly influences revenue and customer satisfaction. This can be observed as the external effect of good quality. If a customer has nothing to complain about he or she will most likely buy the product again. For pharmaceutical products, quality has an even bigger meaning. The supply of low quality products can be a threat to the health of human beings. Therefore, the quality performance objective is to ensure a high quality standard independent of performance fluctuations. The operational goal is to maintain the right-to-operate the business.

The second aspect is conformance quality which relates to the effects of good quality inside operations. It describes the ability to manufacture products to their defined specification [SL08]. High conformance quality leads to a lower failure rate. This generally saves costs and time for failure corrections, increases dependability and increases the speed of response.

The second performance objective is *speed*. Speed means the time between the beginning of an operations process and its end [SL08]. The external impact of speed is that it helps to respond quickly to customers' needs. This increases customer satisfaction and most likely helps to increase revenue. More important for this research is the positive impact of speed to the internal operational performance. In general, speed concerns costs and risks. Slack, Chambers and Johnston [SCJ04] argue that faster throughput of materials help to reduce inventory costs and risks; faster throughput of information lowers costs. Inside operations speed refers to the elapsed time needed to complete the process steps [SL08]. **Figure 3** illustrates some of the significant process time steps in the drug manufacturing operations. Speeding up the various process steps leads to a faster overall cycle time. For example, if the quality control activities after production can be completed faster, the finished products sitting in the warehouse can then be distributed earlier. This saves inventory, costs and lowers risk.

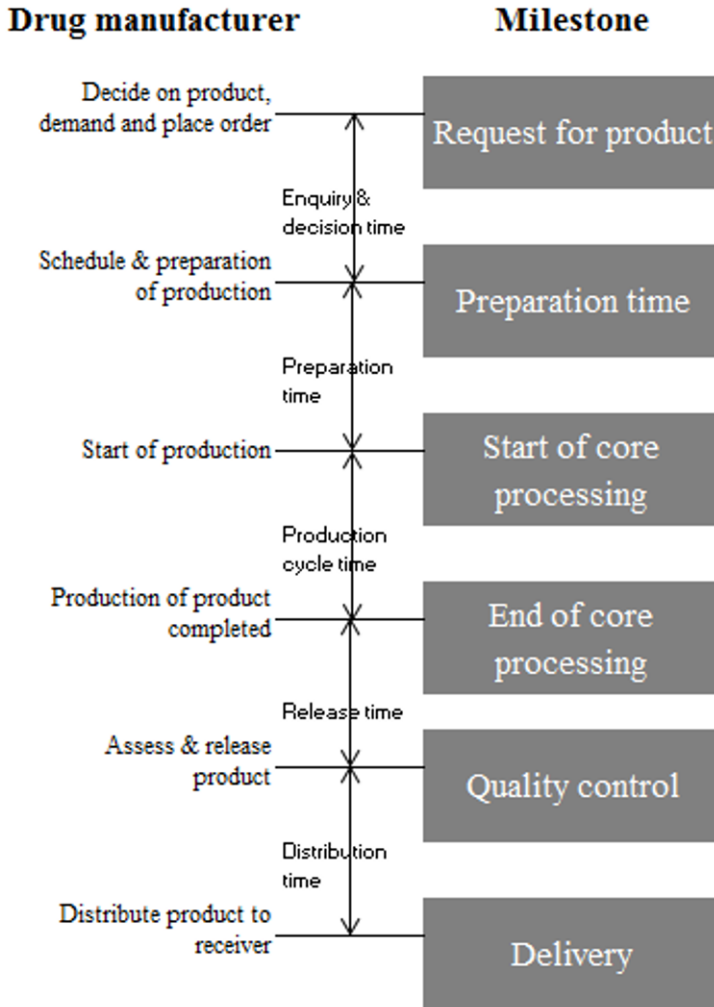


Figure 3, Significant process time steps for the delivery of a drug (ref. Slack and Lewis [SL08], pg. 39)

Another performance objective is dependability. Slack, Chambers and Johnston [SCJ04] defines the term as delivery on time and keeping delivery promises. From an external customer point of view, delivering products at

the promised time helps to satisfy customers and increases the chance of customers returning. From a network point of view, low dependability on one tier of the supply chain increases uncertainty in the entire network, leading to higher inventory and overall lower product availability [CM10]. For multi-tier networks such as those that exist in the pharmaceutical industry, dependability is a crucial operations and supply chain performance objective.

Inside the operations, dependability saves costs by giving an organization high stability [SCJ04]. Higher stability lowers uncertainties and risks and drives down costs.

Flexibility is another important performance objective. It helps to mitigate risks and to respond to changes [CM10]. Slack, Chambers and Johnston [SCJ04] define flexibility, from an operations point of view, as the ability to change operations in some way. They introduce four main types of flexibility that can impact operations performance: mixed flexibility allows the organization to offer a wider range of products, product flexibility enables the organization to provide more customization and innovation in products, volume and delivery flexibility allows the organization to cope with volume fluctuations. Organizations that are able to quickly adapt their operations to these types of flexibilities are likely to achieve a high customer satisfaction and dependability, reduce risks and thus costs.

The last performance objective is cost. This is mentioned last not because it is least important, but rather because it is ultimately influenced by all other performance objectives. Within operations, all other four performance objectives contribute to reducing costs [SCJ04]. This has been one of the key findings within operations management over the decades. The objective is lowering the costs for producing a product in order to offer products at a lower, more attractive price to customers or to increase profit [SL08]. Improving operations costs has become a major lever for improving the financial result of the entire organization.

In addition to the described five key important performance objectives, some authors consider information exchange to be a sixth objective [KLE07; CM10]. If accurate data is exchanged faster and in a consistent way, the organization is able to respond quicker and more efficiently to changes [CM10]. Kletti [KLE07] emphasizes that the deployment of information technology systems significantly contributes to an improved exchange of information, which in turn influences all other performance objectives.

All of the described performance objectives contribute to the achievement of the ultimate operations management objective listed in **Table 2**: a competitive advantage over other companies [SL08]. Competitiveness relates to the set of customer needs that an organization seeks to satisfy in a superior way better than competing firms [CM10]. In the context of batch record documentation, this could be achieved through performing the process faster so that products could be delivered faster to customers. In this example, the competitive advantage lies in the shorter delivery times of the product.

Another objective of operations management is maximizing the market criteria for success. Voss [VOS86] argues that a company can't be successful in all five performance dimensions. Operations management supports the organization by improving the performance dimension that fits best to the strategic direction. In the previous example, operations focused on speed because delivery times have been the main competitive factor demanded by the market.

Another objective of operations management is increasing productivity and efficiency through enhanced technology acquisition. Adam and Swamidass [AS89] reviewed a large number of operations and manufacturing management literature. One common theme is the strategic improvement of operation performance through the implementation of innovative technology, processes and tools. This can be achieved, for example, through implementation of information technology systems that increase information sharing and automate manual process steps.

It was determined that the achievement of operations management objectives is crucial for the business success. The improvement of operation performance plays a significant role. The deployment of enhanced information technologies is a lever to increase performance.

2.1.2 Operations simulation and performance evaluation

The idea of using simulations and evaluation models to assess the potential performance improvement of a system or process is not new. A definition and description of the most commonly used approaches is given below.

Simulation models

A simulation study imitate a system or process which does not yet exist, it allows the analysis of this system or process, it provides information to the objectives of the research performed and supports decision making. Simulations require a mathematical model that represents the real system; the simulation represents the operations of the system or process [BCN09].

In research, simulation studies are often concluded in the area of supply chain management. Retzlaff-Roberts and Nichols [RRN97] emphasizes the power of simulation studies for measuring the performance of supply chains. Most of these models use simplified material and information flow maps across a supply chain network. The models analyze the effects when simulating different supply chain configurations or process parameters.

Despite the broad use of simulation in supply chain management research, this approach can also be identified in operations management. Here, individual manufacturing systems are modeled as simplified process flows to assess the optimal operations performance for a specific research question. Process simulation in the area of manufacturing can be seen as a dynamic process of creating a manufacturing process flow model or map and testing it until a satisfying configuration is attained [MH13].

Masmoudi and Hachicha [MH13], for example, developed a simulation-based methodology for sizing manufacturing cell machines in a cellular manufacturing system. They identified the optimal manufacturing system configuration through testing different machine sizes, process flows and configurations. Performance indicators such as cycle time, machine set-up time and investment costs were used to compare the different manufacturing system configuration. Furthermore, Pitombeira Neto, and Gonçalves Filho [PNGF10] examined the optimization of cell formulation through simulating the manufacturing system considering multiple objectives.

Abdulmaleka and Rajgopal [AR06] focused on value stream maps to visualize the waste in paper mill operations. Their aim was to remove wasted value within the operational transformation process. They developed a simulation model based on different process maps to contrast the “before” and “after” scenarios in detail, in order to illustrate potential benefits such as reduced production lead-time and lower work-in-process inventory.

McDonald, Van Aken, and Rentes [MVR02] simulate an engineer-to-order motion control products manufacturing plant in order to optimize operational and financial objectives. The simulation model is done through value stream maps for different scenarios. In each map different lean manufacturing approaches were applied to the current manufacturing system. The comparison of the different map simulation was done through performance criteria. In this way it was possible to visualize and evaluate complex operations through simulation.

Performance evaluation models and methods

There are a great variety of mathematical models and methods available for assessing and deciding upon a problem with multiple performance criteria. These approaches vary in the model outline, the solution process and the decision space [RAB11]. Generally, the models are divided between multi-criteria evaluation problems for discrete selection problems and continuous

decision problems in which the decision alternatives are only implicitly known [CHO03].

Figure 4 provides an overview regarding multi-criteria evaluation methods that are prevalent throughout the literature [RAB11; VIN86; CHO03]:

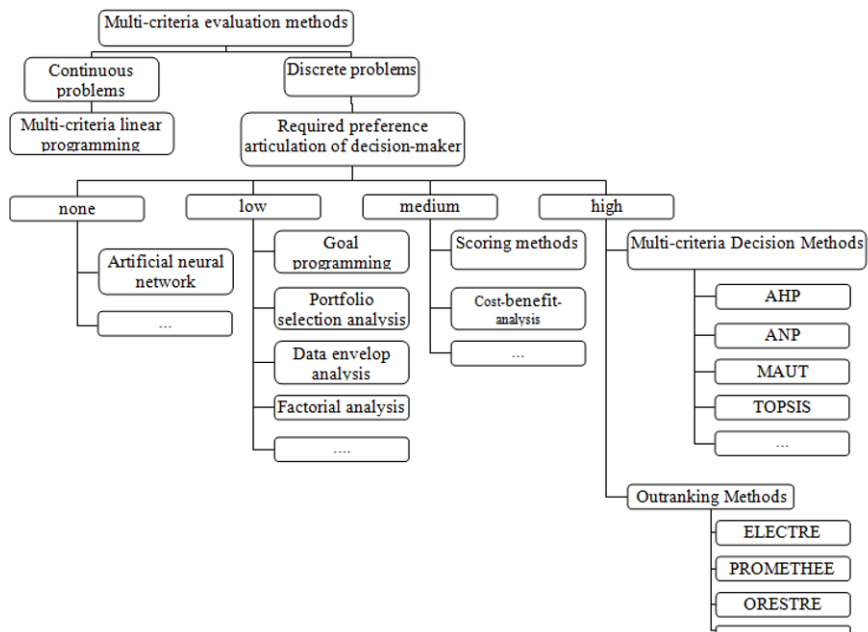


Figure 4, Multi-criteria evaluation methods [own image]

Discrete problems can be further categorized by the decision-maker's preferences; determining the best solution requires his or her' input concerning preferences [CHO03; VIN86]. This information can be defined or estimated beforehand or interactively during the solution process.

Mathematical methods such as goal programming, factorial analysis, portfolio analysis can be applied when the decision-maker's preference is not available, required or shall be avoided. These methods use probabilities and statistical data to evaluate large complex problems [CHO03; VIN86]. How-

ever, these methods come along with high data processing requirements and are therefore not suitable for real-life operations problems.

It is clear that a promising evaluation method for a complex operations system is based on multiple criteria that require input from the manufacturer on his preference and priorities. Therefore, this class of evaluation methods will be focused upon subsequently in further examination.

Multi-criteria decision methods seek to find a solution to a multi-objective optimization problem and ground on representing preferences by means of a utility function (functional modeling) [SWW84]. The most commonly used approaches are Analytic Hierarchy Process (AHP) developed by Saaty [SA80], Analytic Network Process (ANP) by Saaty [SA01], Multi-attribute Utility Theory (MAUT) by Keeney and Raiffa [KR76], the Technique for Order Performance by Similarity to Ideal Solution (TOPSIS) by Hwang and Yoon [HY81].

The AHP method is often applied to solve complex multi-criteria problems. The idea is to decompose the problem into a hierarchy of smaller sub-problems [SA80]. The decision-maker then compares these sub-problems to one another based on their meaning to the overall problem and his preferences. The ultimate decision is then made based on the comparison result.

Outranking approaches, as another class of approaches, consider a finite number of alternatives, assume that the alternatives are known and that the decision making process is executed under uncertainties in particular uncertainties of the decision-maker's preferences [VIN86; RAB11]. These approaches focus on the modeling of the preference of the decision-maker during the solution process [VIN86]. The Elimination et Choix Traduisant la Réalité (ELECTRE) developed by Roy and Vincke [RV81], the Preference Ranking Organization Method for Enrichment Evaluation (PROMETHEE) developed by Brans, Mareschal and Vincke [BMV84] and other methods like Organization, Rangement Et Synthèse De Données Relationnelles

(ORESTRE) developed by Roubens [ROU82] are the most commonly cited methods in the literature.

In literature outranking approaches can be integrated with benchmarking studies. These methods utilize the outranking evaluation to rank the performance of firms in regards to different performance indicators e.g., financial performance [ALYF08]. The firms with the best-in-class performance results are used for comparison and for others to learn from.

In the last years several software packages have been launched facilitating the calculation process. These tools support the weighting and ranking calculation process for different indices. However, most of these software programs such as D-Sights, MatLab and Minitab require the input of the evaluation model and then process the calculation through a contained algorithm. For integrated operations system evaluation the support through proper software is limited. There is no sophisticated tool available that fully supports the evaluation of a complex, integrated operations management problem.

Evaluation methods supporting the information technology selection process of manufacturers

According to Xu and Huang [XH09] multi-criteria evaluation models offers a great tool for organizations that need to evaluate the potential performance improvements through the use of IT applications. In their model, they evaluated how the operations performance of several manufacturing companies in the paper industry can be improved through the deployment of a MES system. The model is based on a hierarchical multi-criteria framework and uses fuzzy programming to calculate the capacity of possible performance improvements through the MES deployment. Their hierarchical index evaluation system comprises multiple tangible and non-tangible indicators which were totaled up to the overall performance improvement.

Kletti [KLE07] introduces an outranking evaluation model for different MES modules. In his model, he links the functionalities contained in different

MES module to their potential of improving performance objectives such as cycle time, machine productivity, personal productivity and on-time delivery. The importance of the different performance objectives have then been evaluated through paired comparison based on the preferences stated by the decision-maker.

Raab [RAB11] focuses on a multi-criteria evaluation model to assess temperature monitoring systems supporting the technology selection process of actors in cold pork supply chains. A metrics with organizational, technical and functional indicators was developed. The evaluation of the most suitable temperature monitoring systems for the different application scenarios and types of meat supply chains has been done through an outranking method.

Chao and Li [CL06] developed a hierarchical criteria framework to evaluate and select the most suitable MES application considering functional and vendor specific criteria. They enhanced previous hierarchical models through the consideration of interdependences between their criteria. This ANP model proved to be very efficient when using mutually dependent evaluation criteria for performance evaluation.

A holistic evaluation framework for MES applications was developed by the MESA [MESA11; MESA12]. Their model aligns key performance indicators (KPI) at the operational, financial and business level into an evaluation metrics. Their model basically integrates different company levels top-down from corporate enterprise goals down to operational KPI level. Several examples of possible metrics with special focus on operational KPIs are presented. The improvements of these operational KPIs through MES deployment and the resulting impact to the next higher business level are discussed in a descriptive and mathematical way.

In addition to these examples, there are many other authors that use multi-criteria evaluation models to evaluate performance improvements and in-

vestment needs for other information technology systems, as illustrated in **Table 3**.

Table 3, Summary of literature review on information technology evaluation methods

Source	Research on	Methods/ Approach
Xu and Huang [XH09]	Designed an production evaluation model based on an index system consisting of multiple indicator to evaluate the performance improvements in the paper production through MES deployment	Quantitative and qualitative evaluation using AHP
Sundarraaj [SUN00]	Develops a strategic management framework for evaluating the deployment of enterprise information technologies on a strategic and operational level. Several methods for evaluation of criteria are introduced: <ul style="list-style-type: none"> • analytical hierarchy process; • data envelopment analysis ; • expert systems; • multi-attribute utility theory ; • outranking; • simulation; • scoring models 	Literature survey
Stockdale and Standing [SS06]	Propose an interpretive evaluation framework for information technology systems investments considering process, content and context dimension	Interpretive approach
Qi, Li and Song	Development of an index system for manufacturing information engineering	AHP for multi criteria

[QLS06]	systems to evaluate the implementation ability. The maturity degree of manufacturing information engineering systems was calculated by using fuzzy comprehensive evaluation.	decision making
Zandi and Tavana [FT11]	Develop two phased model for evaluating IT investments prioritized to the needs of the company. The model uses real option analysis for prioritizing the value of different IT investments. The risks associated with each investment are quantified through fuzzy analytic hierarchy process. Both dimensions (value & risk) are integrated to determine the most valued IT investment using a fuzzy preemptive goal programming model.	Mathematical Fuzzy goal programming model
Powell [POW92]	Study of papers, journal, studies on methods for information system evaluation	Literature review
Chao and Li [CL06]	Development of a model to evaluate MES considering functional and vendor specific criteria. The model takes the feedback and interdependence between factors into consideration and allows a decision on the most suitable MES system for the needs.	Analytic network process for multi criteria decision making with feedback and interdependence between factors
Kletti [KLE06]	Discussed an evaluation model for MES application functionalities contained in different MES modules to their potential	Outranking method

of improving performance objectives		
MESA [ME- SA11; MESA12]	Design an holistic framework for performance evaluation through MES based on a top-down metrics from corporate goals to operational KPIs	Descriptive method and mathematical formulation
Raab [RAB11]	Developed a multi-criteria evaluation model to optimize pork supply chain performance through the deployment of different temperature control tools	Outranking method

It was determined that integrated multi-criteria evaluation models are a concept for the evaluation of performance benefits (output) and investment needs (input) for information technology systems and that these can be used for EBRs evaluations.

Performance evaluation criteria

An EBRs deployment can influence the performances in various parts of an operation. A broad set of multi-disciplinary criteria is therefore useful. The quality of the evaluation is directly related to quality of the chosen criteria. Selecting the right evaluation criteria and indices is therefore crucial [XH09].

There are various criteria from different experts and organizations available in today's literature for the evaluation. The most commonly used areas of evaluation are operational, financial and functional; the organizational dimension is often lacking.

In the past, the MESA provided a metrics for evaluating MES applications based on the fulfillment of seven functional requirements [MESA97]. These functionalities were then evaluated based on their performance impact in the plant. The more recent MESA evaluation metrics for MES application [ME-SA12] integrates operational and financial metrics. The total number of KPIs

is too extensive to list here. The most important operational KPI's in these metrics are manufacturing production cycle time, overall equipment effectiveness (OEE), work-in-process inventory, downtime in proportion to operating time, time to make changeovers, manufacturing costs as percentage of revenue and return-on-investment.

Lenich [LEN08] describes potential performance improvement through EBRS deployment through different evaluation indicators in five dimensions: quality, throughput, operation and maintenance, capital as well as availability.

Xu and Huang [XH09] considered various influencing indicators related to the planning and production processes in their evaluation. The indicators are divided into five dimensions: integration, production, quality, resource utilization and cleaner production. The integration dimension include indicators such as the level of cooperation, the degree of information exchange, the quality dimension included rejection rate, program completion rate and qualification rate. The production dimension incorporated order fulfillment rate and balance production rate. The resource utilization dimension included resource utilization, equipment failure rate and material consumption rate.

Chao and Li [CL06] evaluated the deployment of a MES system through a functional, technical and supplier related dimension. The technical dimension considered indicators such as flexibility, reliability, ease of use, security & compatibility and vendor related criteria such as time, cost, implementation capability and support.

Slack and Lewis [SL08] used various evaluation criteria in three dimensions for information technology acquisition decisions. From a market requirement perspective, they used criteria such as quality, cycle time, dependability, production flexibility and costs. Except for dependability, these criteria are those that are most commonly used in all models. From a financial perspective, they propose return of investment for the implementation and necessary

adaptions. Lastly, from an operations resource capabilities perspective, they use difficulties in moving, copying and substituting as evaluation criteria.

Benson and McCabe [BM04] suggest a benchmarking system consisting of six KPIs for performance evaluation of pharmaceutical companies. They include stock turn, On-Time-in-Full (OTIF) deliveries, Right-First-Time production, OEE, cycle time and safety per 100000 hours. They focused on operational performance evaluation; organizational factors have been neglected.

Kletti [KLE07] derives a holistic evaluation model for MES systems from the ‘magical triangle of objectives’ comprising time, cost and quality. In his model, costs are evaluated through indicators such as implementation costs (namely license fee, hardware, validation, engineering, administration, master data set-up and migration, planning, external support) and running costs (maintenance, IT support, user training etc.). All indicators are then integrated into a Return-on-Invest calculation. Time and quality related indicators are cycle time, OTIF, production flexibility, product quality, OEE, productivity, inventory, data and process transparency, % of meeting customer requirements (satisfaction).

In conclusion, it was determined that there are several indicators available that can be used for evaluating the performance benefits (outputs) and investment needs (input) for EBRS. In order to select the most appropriate ones further research is necessary.

Collection methods of performance evaluation criteria

The use of performance evaluation criteria requires the collection of meaningful information. Data collection means the process of gathering raw data, reducing and transforming the raw data into manageable information and analyzing this information in light of the particular question [WHI00]. For the evaluation of a complex and manifold problem such as the deployment

of an EBRS system, the application of a variety of different data collection methods and techniques is necessary.

Data collection methods are distinguished between qualitative and quantitative methods. For quantitative methods, the data collection is numerical [WHI00]. The most commonly used quantitative data collection methods are the collection of historic data, statistics, questionnaires, and surveys. The data is often displayed in tables, diagrams and statistics for data analysis. Quantitative methods, on the other side, collect data in non-standardized formats and analyze the data through descriptions and concepts [WHI00]. The most commonly used qualitative data collection methods are interviews, observations, and focus groups discussion. A comparison of the most widely spread methods is illustrated in **Table 4**

Table 4, Advantages and weaknesses of data collection methods

Data collec- tion method	Advantages	Disadvantages
Survey	<ul style="list-style-type: none">• Good for descriptive data• Cover wide range of topics• Relatively inexpensive• Can be analyzed using a variety of existing software	<ul style="list-style-type: none">• Self-report may lead to biased reporting• Lack in-depth information• Lacks information on context
Interviews	<ul style="list-style-type: none">• Yield richest data, new insights• Face-to-face contact with respondents• Explore topics in depth• Questions are clarified immediately	<ul style="list-style-type: none">• Expensive and time-consuming• Need well-qualified interviewers• Respondents may distort information• Flexibility can result in

	<ul style="list-style-type: none"> • Flexible in administering interview to particular individuals 	<ul style="list-style-type: none"> inconsistencies across interviews • Large volume of information make it difficult to transcribe
Observations	<ul style="list-style-type: none"> • Information about behavior of individuals and groups • Observer can understand situation/context • Identifying unanticipated outcome • Flexible setting 	<ul style="list-style-type: none"> • Expensive & time consuming • Need well-qualified observers • May affect behavior of participants • Selective perception of observer may distort data • Behavior observed may be atypical
Focus groups	<ul style="list-style-type: none"> • Immediate ideas & rich response • Single subjects can be covered in-depth • Volume of information is manageable 	<ul style="list-style-type: none"> • Facilitators need to be able to moderate and control group • Time consuming & much coordination • Participants may be hesitant to express true opinions in group

The overview demonstrates that each method has its advantages and weaknesses. Westat [WE02] therefore points out that each method shall be selected in the light of the particular evaluation criterion that characterizes the data collection method. A quantitative evaluation criterion such as ‘the number of human errors per batch record’ will most likely require quantitative data collection methods such as obtaining of numbers from archived data. For qualitative evaluation criterion it is the other way around. There a many ex-

amples in today's research in which qualitative and quantitative methods are applied for data collection and analysis.

The collection of process-related data requires in-depth knowledge and a common understanding about the process first. Often the application of process analysis and root-cause analysis methods is previously necessary to obtain the questioned data. Process analysis methods typically analyze current or future processes and systems through mapping and visualization [HU96]. Most of these methods are grounded on the principles of lean management and strive for the identification of waste within the process [WJ03, SL08]. The questioned process-related data such as time, resources and mechanisms can then be obtained as an outcome. Root-cause methods in the context of process analysis are used for a deeper look into the problem or effect in a process [OA08]. Process analysis and root-cause analysis methods; are both important for the collection of data relevant for the determination of process-related evaluation criteria. In today's lean management literature there are a broad variety of existing tools and methods. In the next section the most commonly used methods relevant for the evaluation of the batch record documentation process are introduced.

Process maps or process flowcharts aim at making the single steps and activities within a process more transparent [HU96; FR02; OA08]. Since most processes are cross-functional there are many contributors to a process spanning across the organization. The idea of process mapping is to identify the actual situation and to create an end-to-end representation of the process across the entire organization including roles, resources and responsibilities. There are many examples that show the effectiveness of the technique. Fryman [FR02], for example, illustrated several flowcharts for mailroom operations and illustrated how the method can be used to visualize and improve the in-house mailroom processes.

The advantage of this method is the ease of use. With the help of pencil and paper, a holistic, logic and detailed overview about the process, the number

of involved people and required time can be created [FR02]. The method provides helpful insight to the critical process points that might be the starting point for optimization.

The disadvantages of this method are the time, costs and resources required to generate the map [FR02]. Also, resistances or hesitations of contributors may slow down the process. This has to be carefully taken into account before selecting this technique.

Process maps in the context of batch record documentation are powerful to illustrate the end-to-end flow of information namely the flow of batch record paperwork across the organization and to capture the associated activities. The method provides the basis for collecting data around process time and efficiency. And, process maps are the foundations for defining to-be scenarios necessary for the evaluation of EBRs solutions in the batch record documentation process.

Another powerful lean management method for process analysis is value stream mapping. This method enhances process flowcharts by visualizing the value-adding and non-value action within a process [AR06]. The goal of value stream maps is to identify the waste in the process and to eliminate the non-value adding activities [WJ03]. The method comprises three main steps: selection of the particular process, creation of value stream mapping of current process; and creation of value stream mapping of the improved future state. Thus, value stream mapping is a powerful method for process re-engineering.

Abdulmalek and Rajgopal [AR06], for example, applied the method for identifying the waste in a steel company process. With the help of the method they identified inefficiencies in the company's order and manufacturing scheduling with suppliers and customers. The derived improvements in the planning process led to improvements in cycle time and inventories.

Womack and Jones [WJ03] applied value stream mapping for the intra-organizational optimization of a cola can production.

Both examples demonstrate that the method can be used in a variety of different industries and processes. Another advantage is that is easy to use and the exercise fosters group team work. Some weaknesses exist around the definitions as to which activities can be classified as value and non-value. It can be summarized that value stream maps are a powerful and proven method. In batch record documentation, the method can be used to discover the non-value adding actions in the flow of paperwork and help to develop improved future states that might integrate EBRs solutions.

Ishikawa or fishbone diagram or cause and effect diagram is a method for identifying the root causes to a problem. It has been developed by Kaoru Ishikawa in the 1960th and maps the causes to a particular effect [OA08]. The diagram has the shape of a fishbone. The effect is illustrated at the end of the horizontal arrow. The main causes influencing the effect are illustrated at the end of vertical arrows. The main causes are typically clustered in terms of people, information, materials, equipment and procedures. Sub-causes are mapped as arrows to each main cause. The method is typically processed as a team and brainstorming exercise. The generated ideas are mapped into the fishbone diagram.

The Ishikawa method does not solve problems nor provide data for process evaluation criteria per se. However, it is very beneficial for creating a long list of potential root-causes and categorizing these in a structured way.

The examples of Ishikawa diagrams in today's research are countless. In the context of batch record documentation the method can be applied to investigate the causes of human error occurring in batch records and to examine how these errors can be eliminated through EBRs solutions. This information can then be used to determine evaluation criteria regarding error rates in the batch record documentation process.

In summary, it has been found that the use of performance criteria for the evaluation of the benefits and weaknesses of EBRs solutions requires preliminary work. In order to collect the appropriate data for evaluation the application of various data collection methods are necessary. This needs to be taken into consideration for the evaluation model.

2.2 The Pharmaceutical Supply Chain and Operations Management

In this section, the typical characteristics of the pharmaceutical supply chain and operations management are reviewed with a focus on the manufacturing tiers and the batch record documentation process therein. In order to investigate the first research question, the different manufacturing tiers within the pharmaceutical network are characterized and compared.

2.2.1 Pharmaceutical Supply Chain network

The pharmaceutical supply chain network comprises processes, operations and organizations involved in the discovery, development and manufacturing of drugs and medications [SHA04]. Shah [SHA04] structures the key players as illustrated in **Table 5**.

Table 5, Classification of pharmaceutical operations types (ref. Shah [SHA04]), pp. 929-930)

Type of Operations	Description	Example
Large, research and development-based multinational operations	–Global presence	GlaxoSmithKline
	–Branded products	Pfizer
	–Ethical/prescription and over-the-counter	Roche
	–Manufacturing sites in many locations	Novartis

Large generic operations	–Produce out-of-patent ethical products and over-the-counter products	Teva Sandoz (Novartis)
Local operations	–Operate in home country –Producing both generic products and –Branded products –Producing under license or contract	Ayrton Drugs Manufacturing Limited Midland Pharmaceutical LTD
Contract operations	–Don't have their own product portfolio –Produce either key intermediates, –Active ingredients or even final products –Providing outsourcing services to other companies	AAIPharma Services AbbVie's Contract Pharmaceutical Manufacturing
Drug discovery/ biotechnology operations	–Relatively new start-ups –No significant manufacturing capacity	Ariad Sarepta

Even so this examination does not specifically focus on a specific type of operations, most of this examination will be relevant for the first three groups due to their size of operations and processes used therein.

The typical pharmaceutical supply and manufacturing network consists of multiple nodes as illustrated in **Figure 5**.

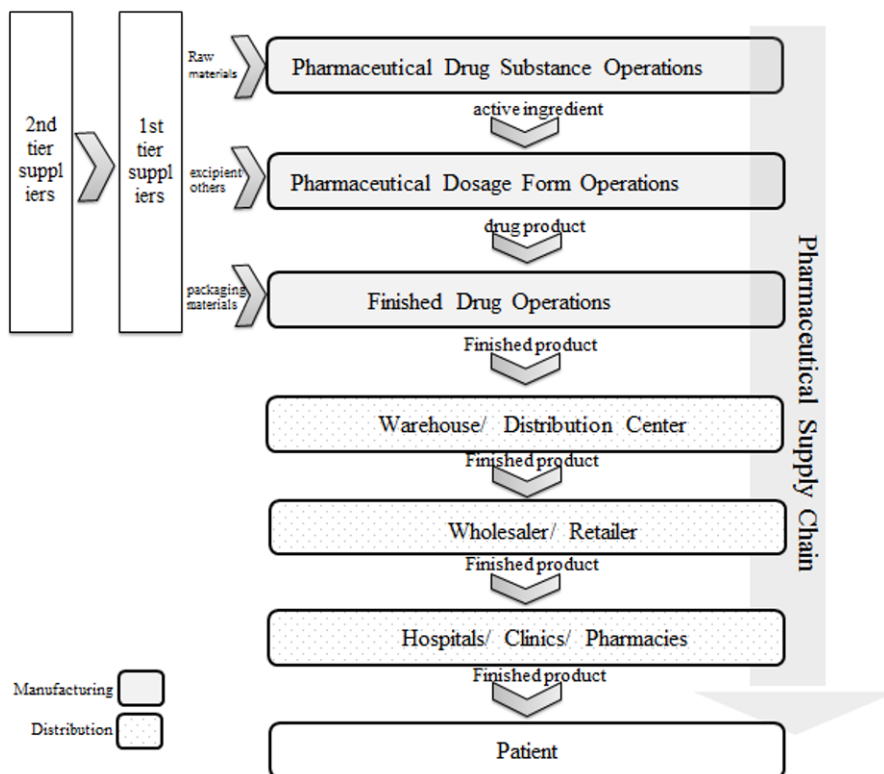


Figure 5, Typical pharmaceutical supply chain [own image]

As illustrated above, the typical pharmaceutical manufacturing chain is divided into three main tiers which represent the main steps of the entire drug manufacturing process: primary manufacturing of the active pharmaceutical substance, the secondary manufacturing of the drug dosage forms and the tertiary manufacturing of the finished drug [FB10]. The distribution part embraces warehouses, distribution centers, wholesaler, pharmacies-retailer, hospitals and links the facilities with the patient.

In the further examination, the focus shifts to the manufacturing piece of the pharmaceutical supply chain, since this is most relevant for the

manufacturing documentation and the batch recording documentation process.

2.2.2 *Pharmaceutical Operations*

Inter-organizational decoupling

Based on the definition provided earlier in this chapter operations management looks at the transformation process of products and occurs internally within the organization [STE12]. Consequently, one could think of the three pharmaceutical manufacturing tiers illustrated in **Figure 5** as one manufacturing operations.

However, primary and secondary operations are basically decoupled in real life by large inventory between both tiers [PMP11]. And, primary and secondary manufacturing locations are often geographically separated [SHA04]. Shah [SHA04] explains that tax and transfer price optimization within the company are often the reasons for this. A typical pharmaceutical manufacturing network has more secondary manufacturing sites than primary ones. In this way the local or regional markets can be better supplied.

Additionally, Kayser [KAY02] mentions that there are technical, process and regulatory differences between the tiers that require pharmaceutical enterprises to separate their operations at least into different buildings. Opposing working procedures make it mandatory to have separate production areas; for example, the isolation of bacteria from soil samples in the primary manufacturing and the sterile manufacturing of parenteralia in secondary manufacturing.

The tertiary manufacturing, the packaging of the bulk product, typically takes place at the same location as the secondary manufacturing location or geographically separated at a contractor's site.

As a result of the organizational and geographical separation of manufacturing facilities, the pharmaceutical manufacturing can hardly be considered as one operation but rather as a network of separate manufacturing operations that supply and/or deliver products, services and information to one another [PMP11].

Separation of batch record processes

The organizational decoupling in pharmaceutical industry also affects the batch record documentation process. Three aspects are essential.

First, batch records exist in every pharmaceutical operation on every manufacturing tier since they are legally required [CW00].

Secondly, batch records are not directly linked with each other across different manufacturing operations. There are single batch records for cells banks, final bulk products and final drugs [WHO11]. However, every batch record must contain a list of the raw materials used in production with the suppliers' batch number to ensure product traceability.

Thirdly, the decoupling of the manufacturing tiers and their different characteristics lead to the fact that each manufacturing tier can deploy different EBRS solutions. For example, the replacement of paper records through an EBRS in primary production does not necessarily lead to the implementation of EBRS in secondary manufacturing.

Because of this separation, it was determined that for the evaluation of an EBRS system an intra-organizational perspective should be considered. The inter-organizational perspective between the different manufacturing tiers is neglected, since the process can be organized separately and implementation decision made, independently, one from the other.

Inter-organizational manufacturing strategies

Based on the definition provided earlier in this chapter supply chain management aims at maximizing the overall supply chain performance and not the performance of single operations [CM10]. In the context of EBRS implementation, it is necessary to evaluate just to what extent the improvements within one operation contribute benefits to the network as a whole. To further examine this topic it is necessary to look deeper into the alignment and the strategies of the manufacturing tiers.

Push and Pull manufacturing: The traditional manufacturing strategy in the pharmaceutical industry is a push production [SRW06]. A push system executes processes in anticipation of a customer order while a pull system initiates processes in responds to a customer order [CM10]. This means a push system operates on forecasted and not on actual customer demand.

With the mentioned challenges in pharmaceutical industry today and the growing need to improve efficiency and agility the manufacturing strategies have changed over time. While the primary manufacturing of the active ingredient continues to be controlled through a push principle based on a long-term forecast, tertiary and sometimes also secondary manufacturing have begun operating based on a pull system [SRW06]. The manufacturing orders in these systems are done based on a specific customer order.

The decoupling of the manufacturing tiers in the pharmaceutical industry made it possible that the final manufacturing tier is rather agile responding quickly to small country-specific wholesaler orders while the first manufacturing tier is rather lean producing large orders in long campaigns with high equipment efficiency.

Batch and continuous manufacturing: Most manufacturing processes in the pharmaceutical industry are carried out on a batch basis [BC03]. Große-Oetringhaus [GOE74] defines this manufacturing mode as the production of similar products that (i) stem from the same raw materials, (ii) use the

same manufacturing process and (iii) is limited by the capacity of the production process.

The exact quality of the final products may differ from batch to batch but should be the same within the same batch. The main reasons for batch manufacturing are traceability of products, validation and regulatory requirements, scale of operations and technology development [BC03].

Continuous manufacturing is used in steady operations and where safety can be improved by the benefits of continuous manufacturing in form of reducing inventories for example with hazardous chemical materials [BC03].

Discrete manufacturing is used in operations where differentiated and distinct products are manufactured [BC03]. These products are easily identifiable, traceable and ready to be distributed to customers. The advantage of this manufacturing mode is that it can be operated in high volume and low complexity manufacturing but also in low volume and high complexity. While continuous manufacturing typically leads to lower manufacturing costs, continuous manufacturing typically provides shorter manufacturing cycle times.

Typically, the primary pharmaceutical manufacturing is classified to be either batch or continuous manufacturing; the secondary manufacturing is normally carried as batch operations with a few being carried out as continuous operation [BC03]. The tertiary production is typically operated as discrete or batch production.

Inter-organizational performance evaluation: From a theoretical point of view, the deployment of EBRs can lead to benefits on operations and network level. However, the mixtures of different manufacturing strategies within the pharmaceutical supply chain make an evaluation of inter-organizational performance improvements difficult. The benefit levels in

other manufacturing tiers heavily depend upon their manufacturing strategies (push/pull, batch/continuous/discrete).

For example, EBRS can help reduce the overall cycle time of the product throughout operations. The product can be distributed faster to the next supply chain node. However, if the next supply chain tier operates on a low responsive forecast-driven push system, the increased responsiveness becomes unnoticeable and difficult to evaluate.

This also supports an intra-organizational focus of the EBRS evaluation.

Characteristics of primary manufacturing

In the following section the relevant literature about the manufacturing tiers is reviewed in order to identify those intra-organizational characteristics that are relevant for the EBRS evaluation.

The primary manufacturing facility is responsible for producing the pharmaceutical substance, the so-called active ingredient. Normally, this can be done either through chemical or through biotechnological synthesis [WAL03]. In contrast to chemical synthesis where several chemical reactions are used for manufacturing small molecule medicine, biotechnological synthesis means the processing of large molecules [SCH09].

Kayser [KAY02] describes the biotechnological synthesis in two phases: the upstream and downstream phase. The up streaming includes the growing process of the cells in the working cell bank and the generation of proteins from these cell cultures. This process is characterized by the fermentation of cells that are typically derived from living organisms [LLG12].

The downstream process includes the recovery of the therapeutic protein from the cell source and the purification of the generated proteins [KAY02]. During the purification of the proteins all impurities and contam-

inants must be removed through the application of various cleaning processes.

The primary manufacturing process is complex because of the various process steps and the sensitive nature of the intermediate products and finished substances. These are sensitive to environmental influences and thus require tight controls throughout the production, storage and transportation [DEC12]. The control data must be recorded and documented in the batch record.

The manufacturing process is characterized by **long manufacturing process times** with often multiple shifts [SHA04]. Before moving the intermediate products downstream the product quality must be checked, taking several days of **process delays for analytic testing**. Only when products and associated batch records are released the drug substance can be used at the next manufacturing tier. This introduces additional days and weeks of delays in the network and back-up inventories.

Typically, process technology includes pipework and batch equipment [SHA04]. In most cases, the manufacturing runs **highly automated** with large number of automated machines, equipment and information technology [BLU04]. The management of this process technology is complex and supported by information technology systems. There are only few manually operated process steps and material transports within primary manufacturing.

The **material flow** is highly **interconnected** between the work stations [BLU04]. Basically all machines and equipment are connected through pipework. The complexity of such highly automated manufacturing operations gives rise to the integration challenge of EBRS solutions with existing process automation technologies and information technology systems.

Low production volumes cause the need for multi-purpose facilities to cap costs. This in turn means that validated equipment cleaning procedures must be in place to avoid cross-contamination. The cleaning procedures must be recorded in the BR. Downtimes of up to four weeks are needed for cleaning and changeovers, which significantly reduces the equipment efficiency in primary manufacturing and implies campaign manufacturing [SHA04]. For example, it is not unusual to produce the annual demand of a product in one campaign and to stock the materials until next year's campaign.

The productions are typically organized as a push system driven by long-term forecasts and as mentioned before operated in long campaigns [PMP11]. Shah [SHA04] argues that this mode of operations causes low responsiveness and is the reason for the poor dependability performance of many pharmaceutical networks.

Characteristics of secondary manufacturing

Secondary manufacturing is responsible for further processing the pharmaceutical drug substance to produce the dosage form. Secondary manufacturing is part of the downstream process and includes the formulation of the therapeutic protein into the finished product and the processing of the product into the final dosage form, usually in stock keeping units [KAY02].

Secondary manufacturing is typically organized as a Push system [PMP11]. Secondary manufacturing consists of multipurpose production facilities that produce a large number of products and intermediates [PMP11].

The **complexity** of the manufacturing lies in the numerous multi-stage manufacturing steps and specialized work center which often require manual steps and transportation between the work centers [BLU04] and which must be performed under clean room conditions with absolute control over microorganism in case of sterile product manufacturing [PMP11].

Compared to primary manufacturing, the process times for secondary manufacturing are shorter between hours and few days [SHA04]. Before moving the product to the packaging manufacturing, the intermediate dosage form products must be analytically tested and the associated batch record released. This again introduces additional days and weeks of delay in the network.

Typically, process technology includes weighting/dispensing, dryers, filtering, filling equipment [BLU04; PMP11]. In most cases, the manufacturing runs with various specialized machines and equipment [BLU04]. From an IT integration point of view, secondary manufacturing is very complex because of the large number of various and complex supervisor control and data acquisition systems (SCADA) controlling specialized machinery and equipment.

In difference to primary manufacturing, there are more manual operated process steps and material transportations within operations. **Containers** are used for the **material flow** within production. After weighting-dispensing of materials into a container the container is moved from one workstation to the next workstation and processed [BLU04]. Vertical transportations across the production levels make it imperative to check that the correct containers are placed at the correct machines [BLU04]. The checks must be recorded in the Batch Record.

The master batch record states fixed batch size limits, which are related to the container size [BLU04]. The quantities of the materials used in the manufacturing process are based on these limits and **volume flexibility** is relatively **low**.

The **routing flexibility** is **limited** in order to avoid cross contamination of products [PMP11]. This means that even if there are copies of machines and equipment available each product is typically processed on a subset of assigned machines only.

Normally, the production is organized in **campaigns** to reduce the risk of cross contamination, save set-up times and ensure high quality [PMP11]. In this case products using the same pharmaceutical substance are consecutively produced. **Validated equipment cleaning procedures** must be in place to avoid cross-contamination. The completion of the procedures must be documented in the batch record.

The typical manufacturing **layout is a complex flow shop** with specialized machines and equipment [PMP11]. It consists of several rooms e.g., for dispensing and weighting, preparation, filling, visual inspection. This implies that for paper-based batch records the paper must be distributed across the shop floor to collect the manufacturing process data.

Characteristics of tertiary drug manufacturing

The third manufacturing tier, the packaging of the finished drug, completes the downstream process [KAY02]. It includes the labeling, packaging and counting of the finished dosage form products [SS08]. The typical process time of one batch in tertiary manufacturing takes several hours to days.

In most countries there are very strict regulations for pharmaceutical packaging [SS08]. As a result there are numerous product versions with country specific labels, inserts and printed folding boxes. Every packaging has to fulfill regulatory and language requirements of the country, general safety, identity, quality and purity requirements.

Packaging facilities typically consist of one or more packaging lines that can process one product at a time [PMP11]. In comparison to secondary manufacturing, the manufacturing process is often a discrete process; one order after the other is packed with little downtime between the changeovers and with larger number of batches per week [PMP11]. Consequently, there is a higher number of batch records but with less size for finished products than for dosage form products per week.

The packaging manufacturing is typically organized as a pull system [PMP11]. The production acts on incoming orders from wholesalers or affiliates. At this tier the manufacturers have to ensure that all country-specific requirements to the packaging are fulfilled and that the right inserts are packed to the pharmaceutical dosage form product before distributing products to the wholesaler. Each step must be documented in the batch record.

The packaging facility is often connected to warehouses in which finished products are stocked and waiting for final release of the batch record. This can take several days up to weeks. Transportation to the next supply chain tier is of the order of one or two weeks if by sea mode and of the order of one or two days if by air mode [PMP11].

2.2.3 *Comparison intra-organizational manufacturing structures*

The review showed that there are typical structures for primary, secondary and tertiary pharmaceutical manufacturing. Blumenthal [BLU04] argues that these structures influence the benefit levels from implementing manufacturing information technology systems such as EBRS. Moreover, these differences can also lead to different implementation concepts and required investment needs for EBRS.

Blumenthal [BLU04] defined a set of typical assessment criteria to clarify in how far information technology solutions, in his specific case manufacturing execution solutions, provide benefits in a pharmaceutical manufacturing factory. For manufacturing execution solutions, for example, he defined:

- Type of process equipment
- Type of products
- Complexity of products
- Degree of automation in production

- Transports using containers
- Information about equipment status
- Work required to document production
- Material inventory in production (WIP)
- In-process control operations

The typical characteristics of primary, secondary and tertiary pharmaceutical manufacturing are compared through a large literature review. Blumenthal's comparison criteria as well as other supply chain and operations criteria are used for the comparison.

Table 6 summarizes and presents the results from four different perspectives: the operations network, the performance characteristics, the process and material flow and the process technology.

Table 6, Comparison pharmaceutical manufacturing tiers

Category	Char-act-eristics	Pharma-ceutical drug sub-stance Manufac-turing	Pharmaceutical dosage form Manufacturing	Finished drug Manufacturing	Sources
Operations network	Facility location	Focused factories	Multi-purpose facilities with large number of products, specialized by product type	Dedicated areas or facilities	[SRW06] [SHA04]
	Prod-ucts	Pharma-ceutical substance	Pharmaceutical dosage forms (tablets, vials, syringes, ointments)	Finished products for sale (drug carton with blister and labels)	[KAY02] [PMP11]
	Geo-graph-ical scope	Products for global market	Products for regional or global market	Products for regional market	[SRW06]
	Push/Pull view	Push	Push or pull	Pull	[SRW06] [SHA04]
	Facility layouts	Highly automated production with separate areas on one floor	Several rooms for preparation, dispensing, filling, finish; isolated, access controlled; connected to warehousing	Few manual but mostly packing lines in separate area of facility	[SRW06] [SHA04]

Operations performance	Asset utilization	Low	Low to medium	High	[SRW06]
	Responsiveness	Low	Low to medium	High	[SHA04]
	Typical manufacturing cycle times	Long several weeks	Mid 1 – 2 days	Short hours – day	[BC03][KAY02]
	Manufacturing type	Batch or continuous	Batch	Discrete and batch production	[BC03][KAY02]
	Campaign manufacturing/times	Yes/up to one year per campaign	Yes, up to several weeks per campaign	Less common	[SHA04][PMP11]
Process flow	Number of key manufacturing steps	Multiple: substrate pretreatment sterilization fermentation recovery purification	Multiple: formulation filtration filling/ granulation/ drying visual inspection	Few: labeling packaging counting	[BLU04][MAU13][SMS03][SRW06]

Material flow	Typical process flow	Work centers are interconnected through pipework	Series of individual work centers in separate areas	Transportation systems between packing machines	[BC03][KAY02]
	Production volumes per batch	Big volumes (hundreds of liters in small number of vessels)	Large number of SKU in small dosages per SKU	High number of packaging units	[KAY02][CL53]
	Characteristics of material flow	Interconnected through pipework	“Station to Station”; WIP in between	Manual or conveyor between packaging stations	[BLU04][CL53]
	Number of manual material transports within production	Few	Numerous	Varies	[BLU04][BC03]
	Material handling equipment types	Bins, vessels, drums	Vessels, container	Palettes, container	[BLU04][BC03]

Process technology	Auto- mation degree	Very high degree of automa- tion; highly automated process technology	Numerous indi- vidual specialized machines/ equip- ment for each work center	High degree of automation; set of parallel packing lines	[BLU04] [PMP11]
	Process tech- nology	Ferment- ers, closed vessels, pumping systems formula- tion tanks	Compounding vessels, centrifug- es WFI applications, filling vessel, pumping systems, washing ma- chines, filling & capping, , crimp- ing machine, lyophilisation chamber	Blister ma- chines, cartoning machines, laser, labeling machines, transportation systems	[BLU04] [BO86] [BC03] [CL53] [KAY02]
	Num- ber of meas- ured process para- meters	Very high (tempera- ture, pres- sure, agita- tor shaft power, gas, liquid flow rate, CO ₂ , foaming, reactor content volume and mass, pH, oxy- gen rate)	High	Relatively low (e.g. bar codes, quanti- ties, weight)	[BO86]

	IT archi- tecture	Recipe control by means of a DCS, ho- mogenous DCS from one ven- dor, addi- tional batch layer between SCADA and MES	Various, inde- pendent and few complex SCADA systems controlling individual ma- chinery, MES connected to SCADA	various de- signs	[BLU04] [MAU13]
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Until now a generally accepted characterization of the biopharmaceutical manufacturing tiers does not exist. Thus, the description of these typical structures can only be regarded as general and rather abstract patterns; in real-life there may be deviations from this. For this reason the analysis of concrete examples is advisable.

As presented above, the typical operations of pharmaceutical drug substances, dosage form and finished drug differ in several structural characteristics. Two main conclusions can be made in regards to performance improvements through EBRS deployment.

First, the implementation of EBRS technology might lead to different benefit levels depending on the characteristics of the manufacturing tiers. For example, lead-time related improvements through EBRS deployment can provide significant benefits in finished drug manufacturing as the highly responsive and pull-triggered part of the pharmaceutical manufacturing chain; whereas this can be a comparably moderate benefit in the long-forecast driven primary manufacturing.

Secondly, the different characteristics of the manufacturing tiers in regards to process technology, equipment and automation degree can lead to different implementation efforts and scenarios for EBRs technologies. In consequence, intra-organizational aspects are to be considered in the evaluation model.

It was found that even so batch recording occurs on every manufacturing tier of the pharmaceutical supply chain the tiers need to be regarded separately for EBRs evaluation. Organizational decoupling, independent inter-organizational batch recording processes, different manufacturing strategies and various manufacturing tier characteristics lead to different benefit levels and investment needs for EBRs. An intra-organizational evaluation of EBRs implementations focusing on the benefits and investments needs for a particular organization is recommended.

2.3 The role of batch recording in pharmaceutical operations

Good manufacturing documentation is a crucial part of the quality assurance and consequently an essential element of the pharmaceutical manufacturing practice. This sub-chapter provides the reader with an overview about the role of manufacturing documentation and in particular of batch records in the pharmaceutical industry. In order to clarify the terminology used in this work, the chapter starts with a definition of the most commonly used documentation elements, then goes on with outlining the objectives and the requirements of manufacturing documentation and EBRs.

2.3.1 Types of manufacturing documentation

The manufacturing documentation is classified in five different types. These types are defined by the European Good Manufacturing Practice (GMP) guideline and FDA regulation (FDA 21 CFR 211). The five types of documentation can be classified as illustrated in **Table 7**.

Table 7, Types of manufacturing documents

Type of Documents	Definition	Example	Source
Specification	Define the requirements of the materials used in the production of a product and an intermediate product; part of the drug registration content	Product specification	[WAL07], [FB10], EU GMP Guideline (chapter 4.14)
Manufacturing instructions	Define the materials used in production & the production steps. In addition, it includes instructions about process controls and technologies with acceptance criteria	Processing instructions, Packaging and Testing instructions, Master Batch Records	EU GMP Guideline (chapter 4.15), FDA 21 CFR 211 (Section 211.186), WHO Guideline 2011[WHO11]
Procedures	Instructions for performing certain operations	Standard Operations Procedures, Working Instructions	EU GMP Guideline (chapter 4.0)
Protocols	Document the performed instructions and recording certain production steps	Batch Record (or Batch processing record or Batch production record)	EU GMP Guideline (chapter 4.17), FDA 21 CFR 211 (Section 211.188)
Technical Agreements	Document the agreement with supplier for outsourced activities	Contracts	EU GMP Guideline (chapter 4.0)

Out of these five primary types of manufacturing documents the focus will be primarily on two types: First, Protocols in particular Batch Records and secondly, Manufacturing Instructions in particular Master Batch Records.

The **Master Batch Records (MBR)** is a document that determines all required steps and instructions for manufacturing a batch of a specific product [WB10]. The MBR is part of the marketing authorization and registration document of the product. The responsible head of production has to ensure that the correct and complete MBR is in place before the start of production and that it complies with the registration document provided to the external regulatory authorities. There are single MBR for manufacturing a cell banks, virus seed lots, intermediates, final bulks of the pharmaceutical drug product and finished pharmaceutical product [WHO11].

The Batch Processing Record or **Batch Record (BR)** is a protocol used on the shop floor to record procedures, operator names, quantity and type of each material used during the operations and the status of each step in the manufacturing process [IOV03]. The BR contains this data for one specific batch that is processed in production. This includes entries, texts, graphics and numbers. The BR must be linked to the proper MBR for the specific product.

In the literature there are two types of batch recording approaches [LEN08; ROE08; WB11; CW00]: paper and computer-aided records. **Paper-based batch records (PBR)** use paper for recording and storing the manufacturing batch data. Operators on the shop floor collect relevant data on sheets of paper. Computer-based batch records or **Electronic batch records systems (EBRS)** use computer system for data collection [CW00].

Next to the already mentioned manufacturing documents **Secondary manufacturing documents** are created during the production of a pharmaceutical product. These secondary documents are not part of the batch record; it represents mandatory documents that belong to the complete batch docu-

mentation [WB10]. **Figure 2.12** provides an overview of secondary manufacturing documents.

The secondary manufacturing document must contain a reference to the associated batch record. For example, the manufacturer must be able to prove that the machines used for the production of a specific batch were correctly maintained and the operators trained. The secondary manufacturing documents can ideally be integrated in EBRs.

Any manufacturer needs to control the pharmaceutical quality of the product and the stability of the process [BO86]. For this the manufacturer needs to document all quality control related activities. These **Quality control documents** are not part of the batch record and must therefore be closely interfaced to the BR [WB10]. The main quality control documents are control reports of starting materials, sample and testing procedures, and validation reports. The complete list of quality control contents can be seen in **Figure 2.13**.

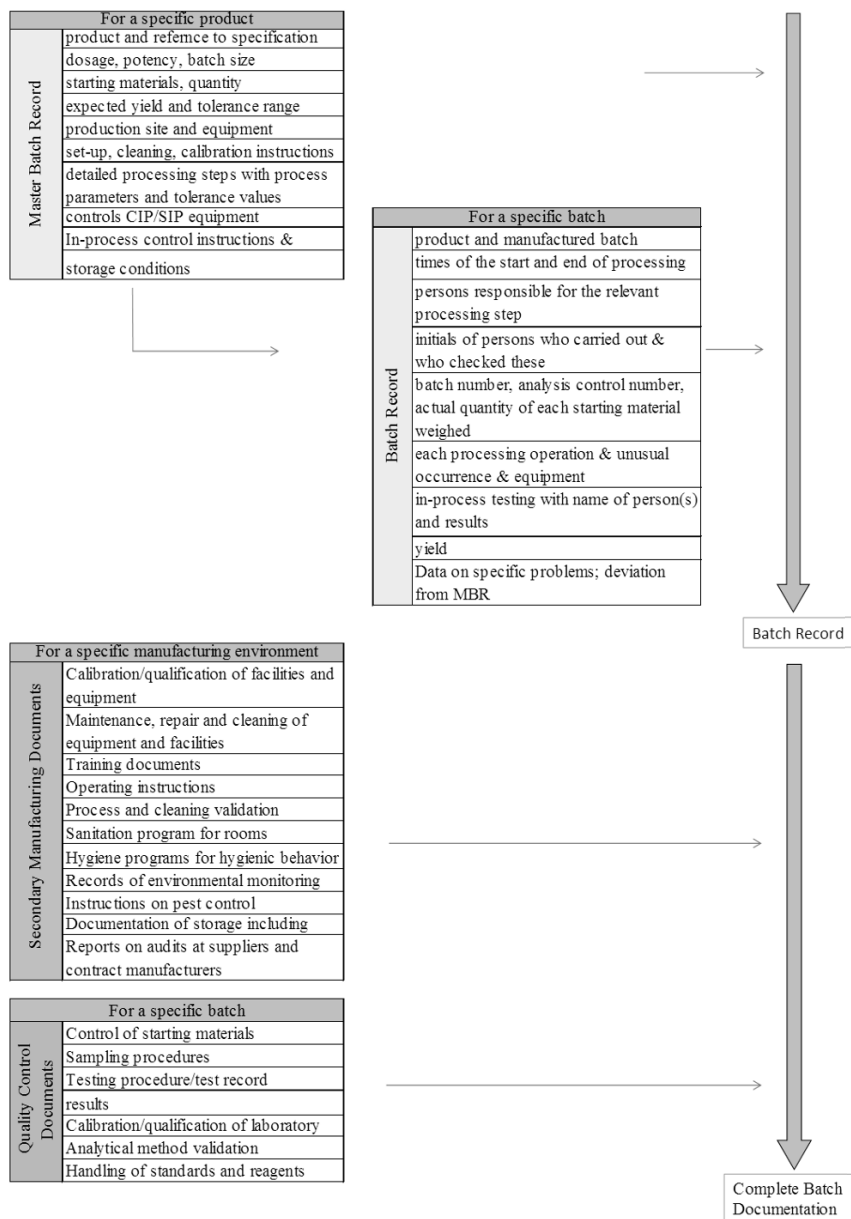


Figure 6, Overview Batch Record & Complete Batch Documentation [own image]

The **Figure 6** provides an overview about the different documents that are contained in the Batch Record and in the Complete Batch Documentation and their content. The format design, the use and storage of these documents depend upon the manufacturer. Some manufacturer will bring all of the documents mentioned above together; some other will keep them separately.

The content of the MBR is defined in the EU GMP Guideline chapter 4.0. The MBR can be seen as the parent document of the BR. The MBR contains step-by-step production instructions for manufacturing a specific product including starting materials, equipment used in production, locations of production, manufacturing dates and operators [WHO11]. The MBR has blank entry spaces to record the data during production, to sign and date all entries at the time the action is taken, and cross-references to all supporting Standard Operating Procedures (SOP) and operations.

The content of the BR is defined in the EU GMP Guideline chapter 4.0. The BR is a copy of the MBR template that contains the order-related and dynamic information for a specific batch. It contains the filled in data entries, signatures from operators, dates, production location, batch number, record and graphs of supporting data (e.g., cleaning equipment records, autoclave records, equipment identification, equipment calibration dates, in-process control quantities and results) [WHO11].

The manufacturing data (MBR & BR) together with secondary manufacturing data and the quality control data represent the Complete Batch Documentation for a specific batch.

Typically, the Complete Batch Documentation comprises many documents and supporting records which are stored in different computer systems (multiple data sources). In case of an inspection, the Complete Batch Documentation must be available and accessible for the auditor. Consequently, manufacturing and quality control data must be cross-referenced and as-

signable to one specific batch. Ideally, all the data is integrated in one system.

2.3.2 *Meaning and objectives of Batch Records*

Laws and official regulations require the documentation of the complete manufacturing, packaging and testing process within the pharmaceutical production. Any manufacturer at any manufacturing tier of the pharmaceutical network must comply with these regulations.

The BR is more than just “pieces of paper”. **Table 8** summarizes the multiple purposes of the BR, which explaining why it is a crucial element within the pharmaceutical manufacturing process.

In regards to the **quality assurance**, the manufacturing documentation and in particular the BR is essential since it contains all batch related data. This allows after the fact data analysis for investigations and provides data for quality prognosis of the future production process.

In regards to **regulatory compliance**, the BR is essential in particular from the view of external authorities such as FDA, EU Commission. An inspector can only draw conclusion about the running of a production process and quality of the manufactured batch from the associated documentation. In fact, the FDA emphasizes the importance of good manufacturing documentation by saying that everything that was not documented may be construed as attempted fraud [FDA12].

From a **supply chain** perspective, the BR is as important as the finished products themselves, because without complete documentation the distribution and sale of the product is impossible [CW00].

For **manufacturing**, the BR serves as instructions that guide the operators step by step through the production process. It provides transparency and documented control about the process.

Table 8, Objective of the Batch Record

Purpose	Description	Source
Compliance	The batch documentation proves that the batch and all materials used therein were produced in accordance with the product specification and within tolerance limits	[FDA12]
Immediate control over production	With the help of BR all production parameters can be recorded during the manufacturing process and immediately corrected if deviations occur	[WB10]
Guidance	BR ensures that all personnel concerned with manufacture know what and when to do it	[WHO11]
Quality assurance	Precise and clear written documentation prevent errors, define processes, helps in the control and monitoring of production processes and thus allows tracing the history of the batch from the purchasing of raw materials to delivery	[FB10]
Investigations	BR provides records and supporting information and an audit trail that allows investigation	[WHO11]
Data source	Provides data needed for trending, statistical analysis, validation, review	[WHO11]
Decision for sale	BR ensures that authorized persons have all the information necessary to decide about releasing the batch for sale	[CW00] [WHO11]

Traceability	BR is part of the overall product traceability concept in case of product complaints from the market	[WB10]
Liability	The BR is the documented evidence and sole possibility for tracing the batch in case of a recall or for clarification of product liability in case of problems discovered after the release	[WB10]

2.3.3 *Requirements on Batch Records*

Independent from decisions about the most-effective batch recording solution any manufacturer in the pharmaceutical industry must ensure that its solution complies with a long list of requirements. In the following section, the relevant literature concerning the requirements of electronic batch documentation and electronic batch recording systems is reviewed from a regulatory, GMP-related and functional point of view.

Regulatory perspective

There is a broad framework of laws, regulations and guidelines that define the regulatory requirements for manufacturing documentation. Often, these regulations stem from different national and international authorities and are overlapping or complementary in their content [WAL07]. The **Table 18** in the **Annex Summary Batch Record Requirements** which is freely available to download on my/the product site at springer.com provides an overview about the most important regulations and the requirements deriving from this.

This overview completes the review about regulatory requirements for batch recording solutions.

Good Manufacturing Practice perspective

Batch Records must comply with the Good Manufacturing Practice [WHO11]. The GMP requirements are primarily defined by EU GMP guideline and FDA's 21 CFR 210/211 & Part 11. The following requirements have a general nature and are relevant to any batch recording system [WHO11]:

- The MBR and BR must be carefully designed, reviewed and distributed. The content must comply with the specification and product registration documents.
- The MBR and BR documents must be approved, signed and dated by the responsible person. Both documents must not be changed without prior approval.
- The MBR must be regularly reviewed and updated. The alterations must be signed and dated. The superseded, revised versions must be prohibited from use. However, they must be archived for the retention period.
- The MBR must have unambiguous content and be laid out in a format that allows checks easily.
- Generally, all relevant manufacturing data must be complete and error-free. Other basic requirements are conformity, completeness, clarity, comprehensibility, readability, clarity, timeliness and indelibility [FB10].
- The MBR must provide for sufficient space for entries. The entries must be clear, indelible and legible.
- The entries must be recorded when the process step and action is carried out.
- The MBR and BR must be archived according to the existing retention periods.
- The process-related measurements are recorded as actual values. These values must be compared with the target values. If the actual values are outside the tolerance limits further investigation needs to

follow. Consequently, transfer errors shall be avoided when designing BR templates.

Functional system perspective

Chapter 4 of the FDA and EU guideline allows the recording of data with the use of electronic means. This is generally called electronic batch recording. For this, reliable electronic data-processing systems or photographic means are allowed although special requirements must be fulfilled.

The required functions of EBRS are introduced and explained in **Table 19** in the **Annex Summary Batch Record Requirements**.

It was found that there is a long list of regulatory, GMP-related and functional requirements for batch record documentation and batch recording solutions. Paper and electronic batch recording solutions, both need to be compliant with these requirements. In the further work I assume that all EBRS solutions examined later in this dissertation can fulfill these requirements. Any risks and performance losses from incompliant solutions are not in the scope of this examination and will not be considered in the evaluation model.

2.3.4 Batch record documentation process

The batch record documentation process can be understood as the end-to-end process within the pharmaceutical operations integrating the creation of templates, the collection and recording of data, the review and release of the records and the archiving of these [WB11, ROE10]. From an operational perspective, the batch recording process begins with the start of the production order for a specific batch and completes with the release of the batch record.

All these process steps are required by law and valid for any pharmaceutical operations at any manufacturing tier of the pharmaceutical supply chain. **Figure 7** illustrates production order flow and the associated batch record documentation flow throughout an pharmaceutical operations.

As illustrated the batch record documentation process spans across various functions from planning, production throughout quality control. In the following section, the batch record documentation process explained and will where necessary highlight the differences between electronic and paper-based BR systems as well as introduce definitions and terminologies for further examination.

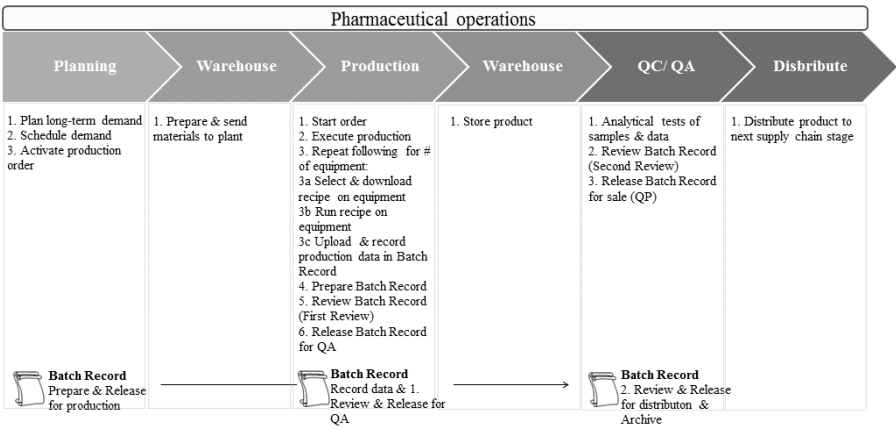


Figure 7, Batch recording process in pharmaceutical operations [own image]

Before process start: MBR templates creation

For a new product the master batch record needs to be created [WHO11]. The MBR is a voluminous electronic or paper file that lists the details of the prescribed production process [PAT01]. The various files have been previously edited, reviewed and approved. Recipes from research and development as well as SOPs developed by manufacturing operations and quality group are the basis for creation [PAT01]. Based on this input, the MBR is authored, reviewed and released by production and quality experts.

One central part of the template creation is the generation of a blank batch record form. This includes the linking of each step of the production route that is the path each product takes through production [PAT01]. From the start of production until finish, every step need to be edited and tolerance parameter defined in accordance with the product specifications. The blank batch record form and other relevant documents are then pulled together into the MBR (see **Figure 6**). Here, the term ‘creating a MBR’ is used to describe the time and resources needed for editing and setting up the MBR.

The review of the MBR means checking and testing the template against the specified procedures in each work center (referred to as ‘reviewing MBR’). For a new product the review is done before the start of the production, for current products the review is done on a need-basis.

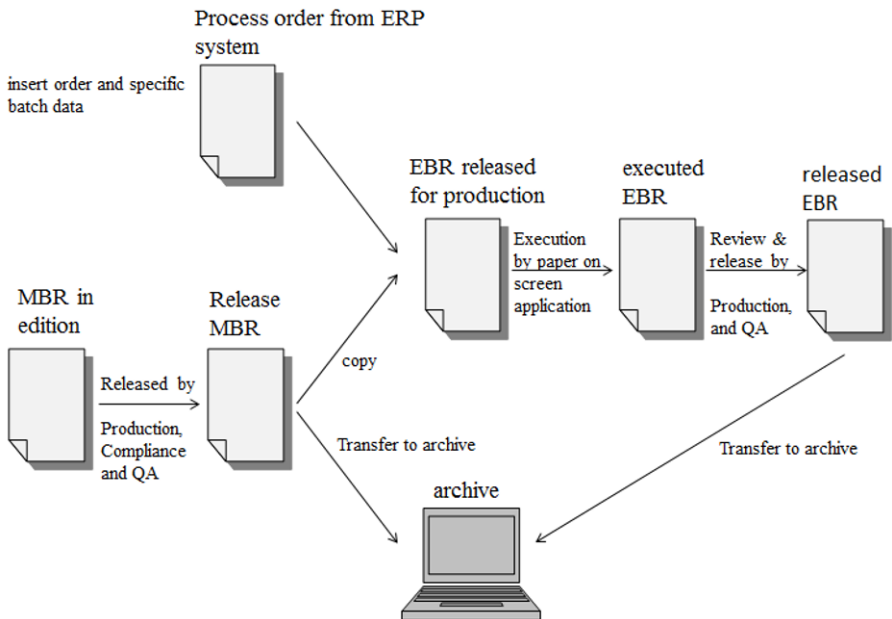


Figure 8, The BR documentation process workflow in a computer-based paradigm (ref. Maurer [MAU13], pg. 4)

The final step ‘releasing the MBR’ means approving it for production. This is typically done by production and quality control personnel as well as the Qualified Person [MAU13].

The creation of MBRs is typically a time-consuming and demanding work. It has to be completed before the order can go to production. The steps for creating MBRs are generally the same between paper based and computer-aided solutions. In a computer-aided paradigm, as illustrated in **Figure 8**, the MBR is typically created, maintained, version controlled and archived with the help of an IT system such as EBRS/ MES [ROE10].

Step 1: order-related information

With the start of a production order, a new batch number is created and a blank template (master template) is converted into a unique batch record for a specific batch. The order-related data e.g. batch number, quantity etc. that is typically coming from the ERP system is added in the BR. This can be done handwritten on paper batch records or electronically through an interface between ERP and MES system.

Step 2: collecting Batch Record data

In this step the batch record is executed which means gathering and recording the relevant data in the BR. The different types of relevant data are illustrated in **Figure 9**.

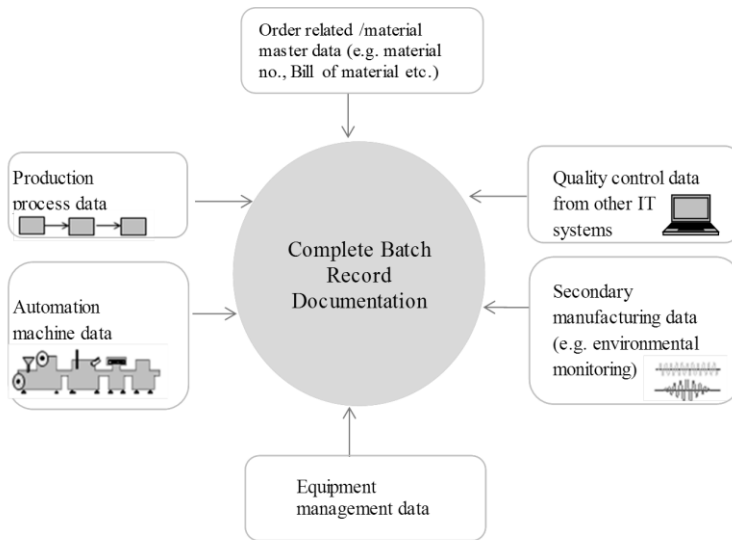


Figure 9, Types of data to be collected during batch record documentation process
[own image]

Paper-based and computer-aided paradigms differ in the way the data is collected.

In the paper-based process, the sheets of paper are distributed on the shop floor before start of production. Operators follow the production process as prescribed in the BR and fill in the required data in the blank entry fields on the BR. For critical entries signatures from a second authorized person are necessary on the paper. Operators read machine and equipment data from the machines and fill the data in the BR. The associated machine log files and offline trend charts are produced and attached to the BR.

In the computer-based paradigm, there is no paper on the shop floor. The process related data is entered by the operator on a computer screen, the so-called ‘Paper-on-Screen’ applications [IOV03]. Electronic signatures confirm the entries [ROE11]. The collection of the machine and equipment

related data depends on the integration level of the EBRS with process automation technology. The higher the integration the more data can be automatically collected from the machines and equipment and transmitted in real-time to the batch record [PAT01]. The same logic applies for secondary manufacturing and quality control data that is stored in other IT systems.

Step 3: reviewing the Batch Record

The Batch Record review is part of the quality control process and must take place prior to the certification of the product [WHO11]. Batch record review means the process step of evaluating the BR content and associated secondary manufacturing and quality control documents.

The process foresees at least three evaluation steps performed by different groups within the organization [WHO11]:

First, the head of production has to ensure that the BR is correct, complete and signed by qualified personnel before sending it to the quality control unit. Secondly, the quality control department and its head of the department have to evaluate the BR together with the Complete Batch Documentation. They have to check if the complete batch documentation complies with the manufacturing and quality specifications and is in accordance with regulatory requirements and GMP guidelines. Thirdly, the Qualified Person (QP) needs to review the BR prior to certification.

Typically, BR review is a complex process and often the longest part of the entire BR documentation process.

Step 4: releasing and archiving Complete Batch Documentation

Releasing the BR is the final step of the process. The QP certifies through a signature, handwritten on the BR or electronically in EBRS that the product was manufactured in conformity with the given requirements and in agreement with the product registration documents. The release must not happen

before all secondary manufacturing data (e.g., environmental monitoring) and quality control data (e.g., analytical test results) are available, properly checked and approved.

The Complete Batch Documentation must be archived in accordance with the retention period and be accessible to inspectors during audits.

Step 5 post documentation process: Trending of data

Trending is a technical analysis that tries to predict the future move of a condition, output, process or other data points based on past data [PMI97]. Batch record documentation is related to trending, since the collected raw production and quality control data of a batch can be used for trending. Trending typically goes hand in hand with EBRs. The data for trending could be batch historian data, system alarms and warnings [PAT01].

The literature review showed the complexity and length of the batch record documentation process. This complexity makes it imperative for manufacturers to strive for improvements in their batch record documentation.

2.4 Background on batch recording technologies and automation design

The idea of using electronic information technology solutions for batch recording is not new [LEN08; KW01]. EBRs are often a sub-set function of MES and closely interact with MES. Today, there are multiple EBRs implementation designs making this topic a complex one. In this sub-chapter, the relevant theoretical background about information technology with emphasis on MES, EBRs and IT integration models is reviewed.

2.4.1 Automation pyramid – the ISA-95 standard model

The integration of EBRS to other information technology systems in the manufacturing environment can be best described through the ISA-95 model, also known as the Purdue Reference model. The ISA-95 model (ANSI - ISA-95) is a standard of the International Society of Automation (ISA) which can be used to evaluate how business processes can be best performed from an information technology point of view.

The model describes the functional hierarchy levels of information technology systems and the embedded functionalities and data objects [TMF08]. It provides guidelines for the integration of enterprise and shop floor data and interfaces for the different system levels. **Figure 10** illustrates a typical automation pyramid with four levels as defined by ISA-95 model [ISA95].

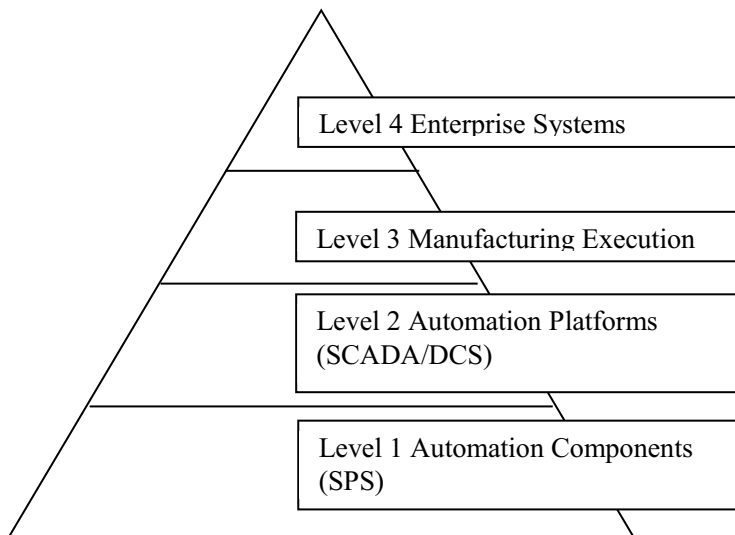


Figure 10, ISA-95 model of automation [own image]

The model illustrates how the manufacturing processes can be best executed and on which levels [MESA97]: From a system point of view, Level 0 – 2 are covered by control systems that are responsible for the process automation [DCS, SCADA, PLC, PCS]. On the first level the sensing and manipulating of the production process and on the second level the monitoring and supervisory control of the process automation takes place. MES and EBRS mediate between automation of the production process and enterprise business level [BLU06]. On this third level, the workflow and the recipes are controlled for producing the desired products and the required records are maintained. On level 4 the basic plan scheduling, material use, inventory and delivery are determined.

The EBRS must be vertically integrated to the process automation technology for realizing a highly automated paperless batch recording process [MON06]. And, the EBRS must also be horizontally and vertically connected to other information technology systems on and above the MES level to realize a paperless Complete Batch Documentation [ROE10]. Since both the vertical and the horizontal integration require large investments it is essential to define the right degree of integration. This aspect therefore needs to be taken into account in the EBRS evaluation model.

The evaluation model is going to embrace the ISA-95 model in so far as different EBRS solutions with different integration depths are simulated and compared. The integration design of the EBRS solutions with other process automation technology and information technology systems is based on the guidelines and standards provided by the ISA-95 model.

2.4.2 *Basic functionalities of MES*

MES is a computer system for the designing, planning, controlling, monitoring and documentation of the business processes performed on the shop floor [KLE06; BLU04]. It covers solutions that are used for optimizing the production activities from electronic order execution

throughout the completion of finished products with all pharmaceutical requirements [MESA97]. From an software engineering point of view, it is an integrated computer system that includes all information technological tools and methods to process a production order [MCCL98].

MES aims to improve manufacturing activities by implementing integrated information flows on the shop floor and through an vertically integrated data management in production [WP03; KLE06]. Furthermore, MES increases security and stability of the manufacturing processes and helps to improve the product quality [BLU04]. MES can support the management of the production processes on a plant wide or enterprise wide level and provide functionalities for the manual, semi-manual and fully automated pharmaceutical manufacturing. MES is suitable for all manufacturing tiers in the pharmaceutical supply chain – from primary to tertiary manufacturing [BLU04].

MES are not isolated systems. One of the most important design characteristics for MES (and also EBRs) is the integration into the entire supply chain IT architecture. Integration is defined as the "connecting of people, tasks and technology to overcome the artificial separation between functions, processes and departments in favor of a single corporate activity [MER09, p.1]". Overcoming this separation through the integration of all data throughout the production and supply chain is a general objective of the business information processing and computer-aided production [MER09; SCH98].

Although the MES concept is now widely used also in the pharmaceutical industry it lacks taxonomy. Sometimes, very different software solutions hide behind this term.

According to the MESA the MES constitute of several core functionalities and interacts with multiple supply chain, in-plant and enterprise systems [MESA97]. The MES model is illustrated in **Figure 11**.

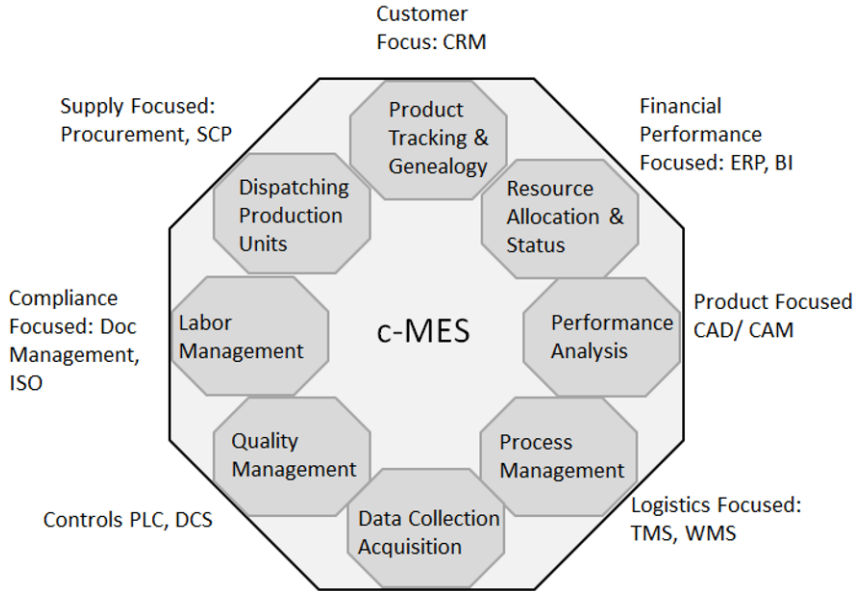


Figure 11, Functional components of collaborative MES (ref. MESA [MESA04], pg. 3)

In conclusion, MES is not a standard piece of software but an omnipresent production “watchdog”, which uses electronic means to query, assemble and disseminate information (data and decisions) electronically [BD98]. It should be understood as software solution for production control as a supplement to existing PPS and ERP systems, enhanced control system for controlling and monitoring of production process automation and IT platform for the integration of software systems of production process automation and production management [WP03].

2.4.3 Basic functionalities of EBRS

EBRS are computer systems or applications supporting the documentation process through the complete production process and enabling a paperless production process [ROE10; NN06]. Over the last decades the technology has made huge progress and EBRS have been replacing the paper-based

collection, recording and reviewing of manufacturing data through a computer system.

The functionalities of today’s EBRs extend beyond electronic batch recording and security functionalities and include administrative functionality of the EBRs such as automated documentation and validation methodologies [GHO12].

One of the key functionalities of EBRs is the workflow-based execution of the batch record. In comparison to paper records, the electronic layouts of the BR forms can be optimized and intelligent elements and functions established [ROE10; IOV03]. Lenich [LEN08] states that this helps to effectively design the user surface of the EBRs and improve the manufacturing workflow. Ideally, the form is designed in such a way that it walks the operator through the manufacturing process without possibilities for wrong or missing entries in the workflow.

Further functionalities of today’s EBR applications are presented in **Table 9** [DE13]:

Table 9, Functionalities of EBR application (example)

Functionalities of EBRs
Paperless processing and documentation of all production activities
Online verification of manual data entry and automatic logging of deviations
Automated support for process analysis (PAT)
Seamless integration of batch execution and data historians/ archiving systems
Modular design of MBR templates, unified process steps enabling a high degree of re-usability
Integration of work instructions based on a library

Flexible maintenance of process parameters, material and equipment rivers

Configurable version control and approval workflows

Automated control and documentation of all production activities of the paperless production

Access by PC and Thin Client via Browser possible, appropriate IT architecture available

Complete process integration through OPC

In Process Control functionality

Batch Review Functionality

21 CFR Part 11 compliance

Historically, the EBRs were integrated in the MES system. This means the functionalities listed above have been subset functionalities of the MES.

Today, there are multiple EBRs design on different level of the ISA-95 automation pyramid and solutions on the market.

EBR applications can be found on the ERP, MES or process control level (SCADA) [ROE10; IOV03]. Also suppliers of document management systems (DMS) provide partially EBR functionality. Here, central database, so called data warehouse, are deployed to collect data from different source systems in a standard format and file [ROE10].

In the pharmaceutical industry, EBR applications are widely used on the MES layer [BD98; ROE10]. However, Roemer [ROE10] points out that the distinctions are fluently and sometimes overlapping. A clear technical classification of EBRs types is hardly possible, since the boundaries are in-

creasingly blurred by different functional scopes and convergence strategies of suppliers.

In summary, the way EBRS is integrated with process automation technology and other information technology systems influences the possible benefit levels of these solutions but also the investment needs. Thus, the technical integration cannot be neglected from the evaluation model. It was determined that the complexity and variety of existing solutions make a holistic evaluation for all EBRS solutions impossible. The scope of the evaluation is therefore focusing on typical generic types of EBRS deployed in the pharmaceutical industry. These generic EBRS/ MES types of systems will be identified, described and examined in the next part of this research.

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