論文 / 著書情報
Article / Book Information

題目(和文)	医薬品生産に関するプロセスライフサイクルエンジニアリングのシステムズアプローチ
Title(English)	Systems Approach to Process Lifecycle Engineering in Pharmaceutical Production
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出典(和文)	学位:博士(工学), 学位授与機関:東京工業大学, 報告番号:甲第9365号, 授与年月日:2013年12月31日, 学位の種別:課程博士, 審査員:関 宏也,山口 猛央,西山 伸宏,田巻 孝敬,渕野 哲郎,仲 勇治,杉山 弘和
Citation(English)	Degree:Doctor (Engineering), Conferring organization: Tokyo Institute of Technology, Report number:甲第9365号, Conferred date:2013/12/31, Degree Type:Course doctor, Examiner:,,,,,,
学位種別(和文)	博士論文
Type(English)	Doctoral Thesis

Systems Approach to Process Lifecycle Engineering in Pharmaceutical Production

(医薬品生産に関するプロセスライフサイクルエンジニアリングのシステムズアプローチ)

by

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Submitted to Department of Environmental Chemistry and Engineering
as a Dissertation for the Degree of

Doctor of Engineering

at the

Tokyo Institute of Technology

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Preface

Intricate modern pharmaceutical business activities strive to achieve lean developments of production processes for desired levels of quality in the lifecycle of processes. To manage suitable business processes in a lifecycle pharmaceutical development, this study builds a framework to handle knowledge and discoveries, which are obtained through pharmaceutical production process development, among activities of process engineering. To summarize major activities and outcomes, we give an overall outline of lifecycle engineering (LCE) applied to pharmaceutical production processes. Then, to identify the structure of information transactions, a detailed business process is logically illustrated as an IDEF0 activity model. This activity model unambiguously frames the hierarchical activities of first the Define desired product performance stage, second the Design product stage, and third the three subordinate stages: Design recipe, Design facility, and Produce. This hierarchical structure represents administration, coordination, and implementation functions. To support continuous improvement of the production process, the model defines a Plan-Do-Check-Act (PDCA) function that is to be performed among overall activities; this function clearly defines not only the horizontal PDCA cycle on an activity layer but also the vertical PDCA cycle between activity layers.

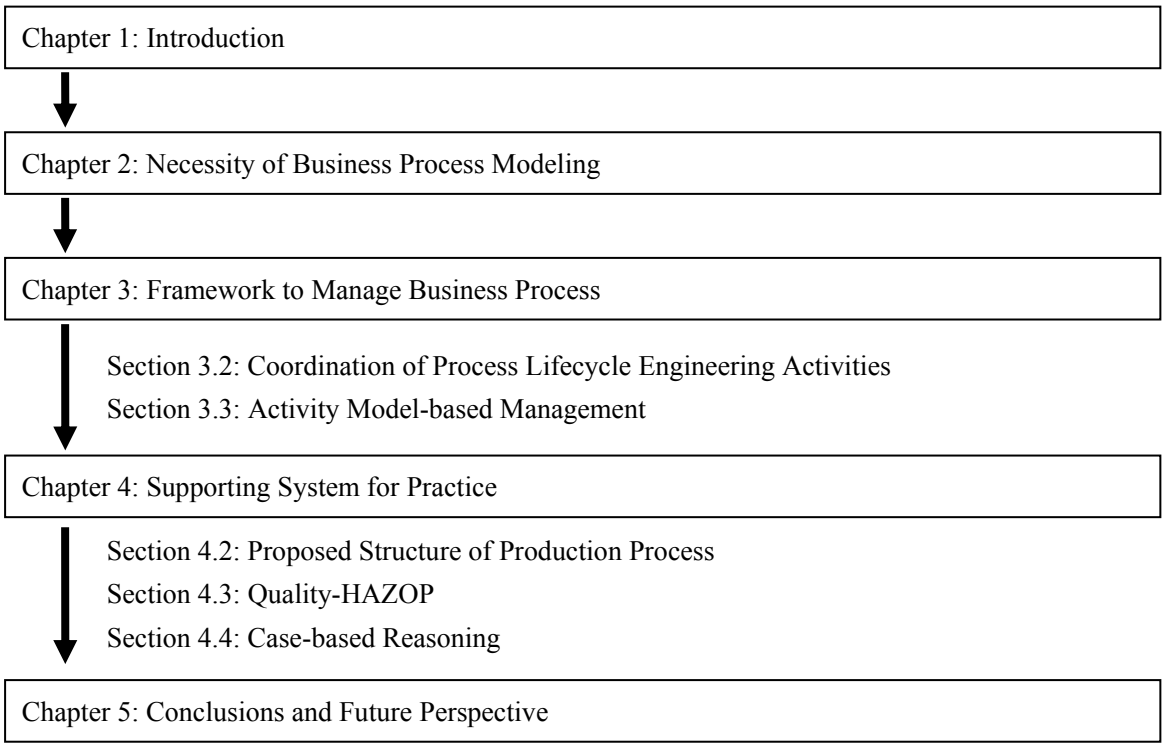
If LCE is implemented and a problem occurs, change management must be triggered. Protocols for the change management are designed in the activity model. The guide forms to support decision making are prepared on the activity model as engineering standards. Decision making, which otherwise depends on personal memories, can be recorded on the activity model using guide forms. The guide forms can be continuously improved by accumulating decision making experiences and improving defects in past decision. This activity model-based approach supports extensive business processes between projects, development phases, and business organizational structures, and thus facilitates a holistic and proactive LCE implementation for continuous improvements in quality.

Availability of this activity model-based framework for change management is demonstrated by analyzing changes performed in an actual company. This case analysis shows that failures in information transactions occur frequently from Production stage to Design recipe and Design facility stages. Therefore, a system named *Quality-HAZOP* is proposed to support the information transactions. Before constructing this system, the structure of a pharmaceutical production process is organized. Process operation and behavior are classified to logically illustrate the relationships of overall process elements of process stage linkage and intermediate elements between input and output. Different views of scientists and engineers are clearly represented. To bridge viewpoints between the recipe scientists and process engineers, two scenarios describing the relationship of product-specific processing parameters and equipment/operation/material-specific processing parameters are designed: the process deviation scenario and the procedural control scenario, respectively. The procedural control scenario includes pathways from errors in manipulative actions to process state failures of controlled states. The process deviation scenario includes pathways from process state failures to deviations in monitored states, performance attributes, and consequent product specifications. The two scenarios are then integrated as the Quality-HAZOP by bridging scenarios with the common items in the process state failures. The Quality-HAZOP can show the overall pathway from a procedural error to hazards in product quality. With the Quality-HAZOP system, bidirectional exchanges of risk information become possible between scientists and engineers.

On the basis of the IDEF0 activity model, a framework is proposed to handle knowledge and discoveries obtained during the lifecycle of a pharmaceutical production process. An LCE on the framework promotes more effective use of knowledge and discoveries, and it facilitates PDCA in overall LCE activities. This framework continuously improves the business process in pharmaceutical production process LCE.

The structure of this dissertation is as follows. After the introduction in Chapter 1, Chapter 2 explains why description of the business process as an activity model is necessary to implement LCE; then the chapter proposes an appropriate structure for the engineering activity model prior to describe the model of pharmaceutical production process LCE. In Chapter 3, the business process of pharmaceutical process LCE is illustrated in an activity model by using the model template introduced in Chapter 2. Then, Chapter 3 explains the activity model-based framework to manage business processes of process LCE. The management of a business process is explained by dividing it into preparation,

implementation, and change management of LCE. Applicability of this framework is shown using actual cases analysis of a pharmaceutical company. Chapter 4 presents a system to support information transactions between recipe scientists and process engineers; such transactions tend to fail without a suitable management system. In addition, a case-based reasoning approach is introduced as a cooperative method in the system to find relations between errors and deviations. Chapter 5 concludes this dissertation with future prospects.



Structure of the Ph D thesis.

Acknowledgement

The thesis is the result of almost four years of research at the Department of Environmental Chemistry and Engineering in Tokyo Institute of Technology. During this time, many wonderful people provided me with scientific and personal support.

I would like to express my sincerest appreciation to thesis main supervisors, Yuji Naka and Hiroya Seki, for giving me the opportunity to conduct this thesis work at their group. They guided my research with a well-balanced amount of critical and creative, broad and in-depth comments.

My special thanks go to Takeo Yamaguchi, Nobuhiro Nishiyama, Tetsuo Fuchino, Hirokazu Sugiyama and Takanori Tamaki who provided kind advice for finalizing this thesis.

My deepest gratitude also belongs to Teiji Kitajima and Rafael Batres who were most dedicated in supervising my work with precious ideas, great enthusiasm and steadfast leadership.

Case-based reasoning in section 4.4 is supported by Junpei Sugiura in Toyohashi University of Technology. He built the concept lattice drawing program from a context table. His contribution is strongly reflected on this study.

Quality-HAZOP concept is co-developed with Takeshi Ishikawa and Yuanjin Ling in Techno Management Solutions Ltd. They kindly implemented the HAZOP on their product, TechmasNavi^{TM}, to demonstrate pharmaceutical production process on written P&ID.

Hierarchical process scenario application, *micks*, is programmed by Naomi Itoh in Kyowa Hakko Kirin Co. Ltd. She took no frustration out on me despite a lot of requests. This application will become a very supportive tool in Kyowa Hakko Kirin Co. Ltd. through her great efforts.

On the occasion of writing this thesis, Yasunori Kikuchi in Tokyo University and Hisami Watanabe in RIKEN provided a lot of advice to me.

Numerous people in Kyowa Hakko Kirin Co. Ltd. supported my research. Especially, Jun Yamaya, Hideya Ohashi, Yutaka Makimoto, Kenjiro Kano, Yoshinobu Konno, Taishiro Nakagawa, Shinji Sakae, and Tetsuji Hayashi counseled and innerved in all times and places.

My deepest appreciation and gratitude is reserved for my family, for all their love, support and their unwavering faith in me.

I sincerely promise to return all kind backup to all of future researchers as well as all of associates above.

December 2013 Hirofumi Kawai

Contents

1 Introduction

1.1 Challenges in Pharmaceutical Industries

In pharmaceutical industries as well as other industries, quality design systems have become important in accelerating the rate of product development. Investment in R&D of pharmaceuticals has increased for over the last few decades. Especially, in biopharmaceutical R&D, expenditure almost doubled from $26.0 billion to $48.6 billion in ten years from 2000 to 2011, as shown in Figure 1-1 (PhRMA, 2013). This rise in investments has been caused by the speedy development of multiple high-quality products; nevertheless, in present industrial paradigm, even faster development is required.

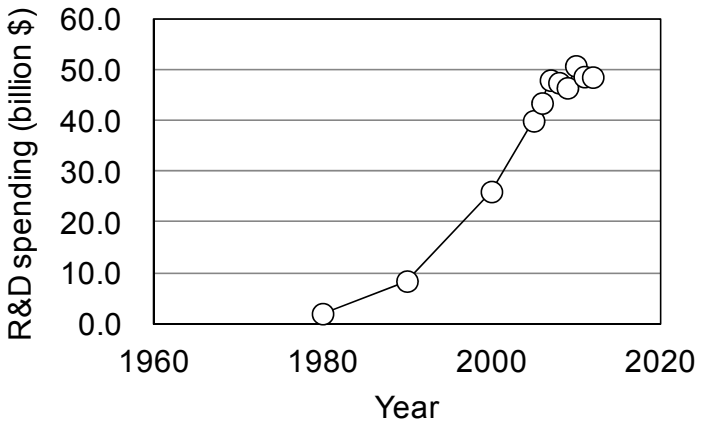


Figure 1-1 Increase in R&D spending analyzed by Pharmaceutical Research and Manufacturers of America (PhRMA). Data from PhRMA industrial report (PhRMA, 2013).

Success rates of pharmaceutical products are lower than in other industries. In chemical drugs, one product typically reaches the market out of 5,000-10,000 candidates at the discovery stage (PhRMA, 2007) (Figure 1-2). In biological drugs, the success rate is one product from 80 candidates (Genia and Justin, 2013). Although probabilities differ by therapeutic class, the average success rate from clinical study to market is 16% for

self-originated drugs and 19% for all compounds (including licensed-in and licensed-outdrugs in addition to self-originated drugs) (DiMasi *et al.,* 2010). Therefore, bringing limited pharmaceutical candidates to market is a risky business. In this situation, pharmaceutical industries have shifted business policies to focus, not only on a few blockbusters with huge anticipated markets, but also on several orphan drugs with limited anticipated markets (Genia and Justin, 2013). Consequently, the number of product pipelines in a company has increased. In order to handle increasing number of pipelines, recent pharmaceutical plants deal with multiproduct and the plant structure becomes complex. In addition to low success rates, long times are required to develop a pharmaceutical product. The drug development period can be divided into discovery and clinical stages before commercialization (Figure 1-2). From drug discovery to market requires 9.5–15 years for chemical drugs (PhRMA, 2013) and an average of 7.7 years for biological drugs (Rajapakse *et al.,* 2005). The discovery stage itself, including drug discovery, product design, and preclinical studies, requires 3–6 years (PhRMA, 2013). The clinical stage is difficult to reduce, because it relies on therapeutic treatment with the drug. Therefore, pharmaceutical industries adopt two strategies to reduce total costs for drug development. First, they shorten the period of the discovery stage. Second, they deliver as many candidates as possible to the clinical stage for first-in-human trials and judge go-no-go as fast as possible to manage the product portfolio (Rajapakse et al., 2005; Federsel, 2006).

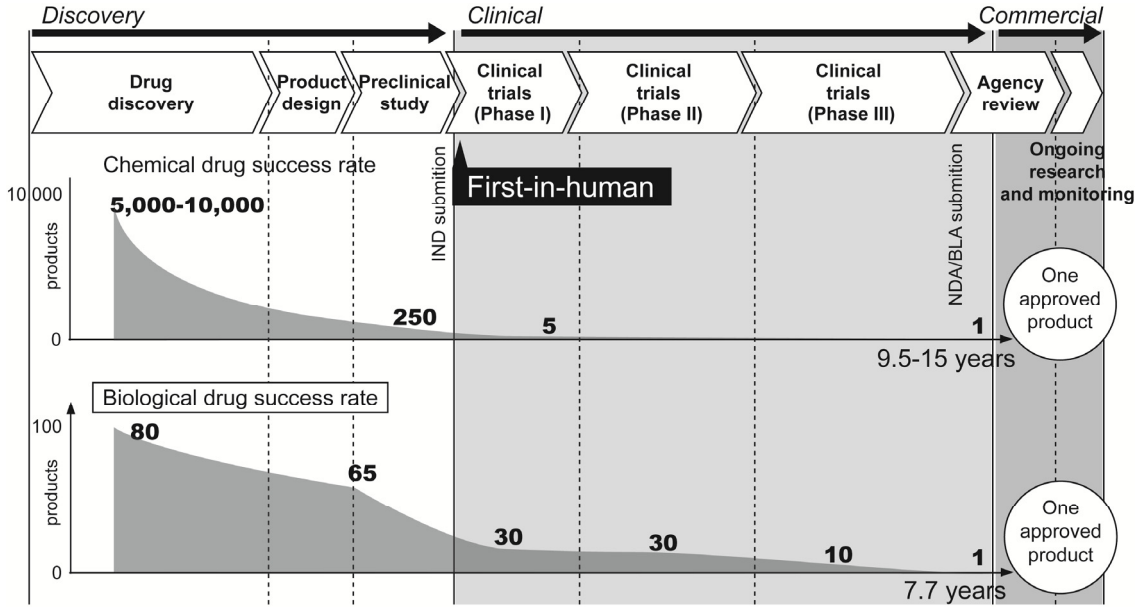


Figure 1-2 Drug development pathway and success rates. IND: Investigational new drug application, NDA: New drug application, and BLA: Biologics licensing application.

Accelerating process development is required not only for early judgment of go-no-go but also for early entry into a competitive market. Pharmaceutical sales over product lifecycles show slow growth rates and precipitous declines (Ellery and Hansen, 2012). Slow growth rates have two causes. First, physicians are understandably reluctant to move patients to a new drug until it has proven its worth. A high risk is involved in moving a sick patient from therapy that is controlling a disease to one that might or might not prove to be better. Second, pharmaceutical companies are severely limited in how much they can promote a new drug until it has been approved for patient use. There is a steep decline in sales once patents expire and is caused by cheap generics or biosimilar drugs that flood the market. To maximize return on investment, pharmaceutical companies cannot afford to spend a long time for process development.

Therefore, a solid production process must be developed within a limited time. However, rushing delivery of investigational drugs using makeshift processes can increase costs due to the risk that many process changes will be needed during late stages. In Figure 1-3, the process development pathway (gray box arrows) is overlaid on the product development pathway (white box arrows). During the discovery stage, processes for preclinical and early clinical products are designed to satisfy early requirements on a product. After that, the process is continuously developed to improve process robustness and to adapt it to large scale production. Since pharmaceutical production, especially biological production, at large scales is time-consuming and expensive, opportunities for trial-and-error testing are limited in a production plant. Since the process and facility is to be fixed before phase III clinical trials are started and preclinical and early clinical trials require few amount of products, opportunities of large scale production to obtain clinical samples are also limited. On the basis of the limited experiences of large scale production and supporting laboratory scale studies, the process is fixed before Phase III clinical trials. If an early process is designed on an ad hoc basis, excessive cost and time would be required to adjust the later process (Farid, 2007). Therefore, a process has to be developed by focusing on future possible expectations. However, since the concept of a given drug is proven after or during the early clinical studies, detailed commercial production plan may not be determined before completing it. It is a specific characteristic of the pharmaceutical industry that requirements on product quality, productivity and commercialization are not clearly decided during the first process development stage. Under these circumstances, it is frequently unavoidable to change the production process from discovery to the commercial stage. Consecutive process

development from discovery to the commercial stage is controlled by lifecycle engineering (LCE) activities. As is obvious, important factors in LCE are not only cost and speed but also product quality. As an alternative of running on *a hand-to-mouth basis*, a systematic approach has to be built to support development of solid production processes through LCE activities.

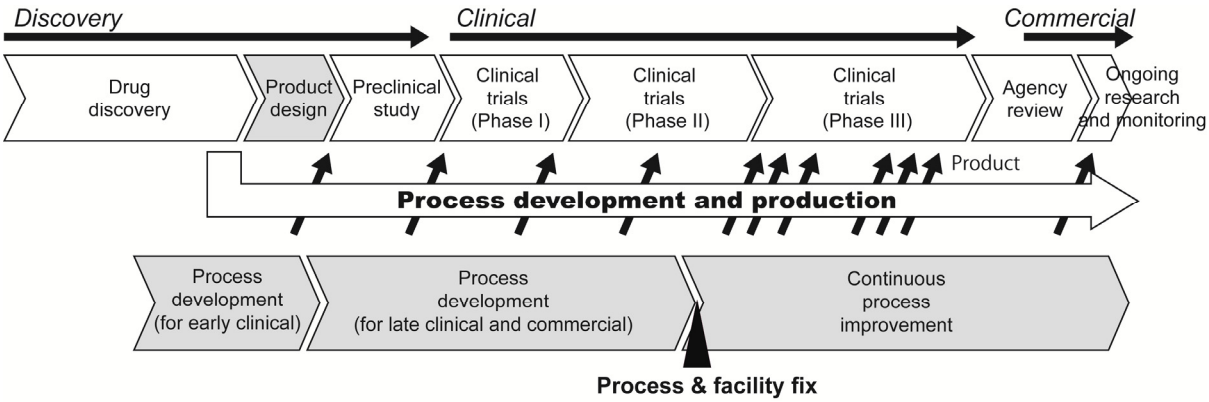


Figure 1-3 Process development pathway on the product development pathway.

In summary, scientists and engineers of pharmaceutical production processes face three primary challenges. First, the quick establishment of production processes is necessary to increase the number of the first-in-human trials and to achieve an early entry into competitive markets. Second, tight investment and scheduling restrict experiences of scientists and engineers with large scale production. Third, product quality specifications, required productivity, and a business plan cannot be clearly determined before obtaining results from first-in-human studies.

1.2 Lifecycle Engineering in Pharmaceutical Development

With rise in investments and development, new problems have arisen; in particular, there is a requirement of systems that enable industries to focus their business activities on quality design. Suresh and Basu (2008) showed that fundamental research in the science of pharmaceuticals product development and manufacturing will not only improve the quality of pharmaceuticals but also reduce the time to market, possibly saving as much as $20–50 billion annually in cost of goods for the entire industry. In addition, such fundamental research helps regulators develop science-based regulatory policies. However, results of

fundamental research on quality design have not been broadly implemented among overall activities because the industry has not developed practical business processes for effectively applying the research findings. Current industries are challenged to design a logical scheme that integrates fundamental research with production knowledge.

Figure 1-4 shows typical business activities in product and process development. This scheme is based on previous studies involving chemical (Sugiyama, 2007), agro-industrial (Sundquist *et al.,* 2000), and pharmaceutical (Basu *et al.,* 1999; Lepore and Spavins, 2008; Nasr, 2007) models. Five activities are included in this scheme: Define product performance, Design product, Design recipe, Design facility, and Produce. Through these five activities, a process is developed to meet requirements on product quality and productivity; the resulting process can be applied to investigational and commercial production.

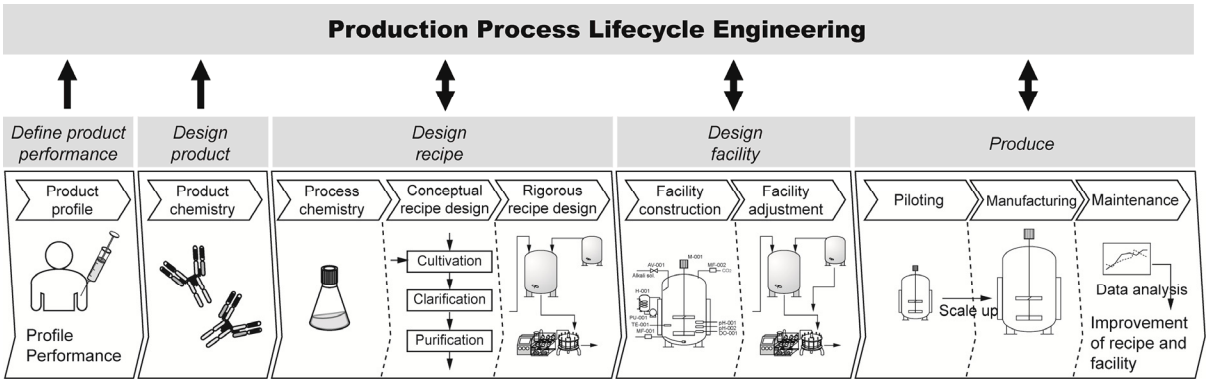


Figure 1-4 Typical business activities in process engineering.

The five activities in Figure 1-4 do not constitute a strict chronological sequence. Business processes occur along different timelines, places and projects have to be managed to achieve the best cooperation among these activities. This management function of business process in a product lifecycle defines lifecycle engineering (LCE). The stage-gate® approach has been proposed as a decision-making system for product development from discovery to market (Cooper, 2008). Although limited business processes could be managed by the approach, it is difficult to use stage-gate® approach to manage overall cooperation in LCE activities.

In the pharmaceutical industry, the concept of LCE is known as *Quality by Design* (QbD). In 2005, at the International Conference on Harmonization (ICH) Q8, the QbD concept was finalized to promote R&D based on quality design (ICH, 2010). According to

the ICH Q8 concept, the quality of pharmaceuticals cannot be tested into products; instead, quality must be designed into the manufacturing process to consistently deliver the required performance. This approach must be based on overall R&D process information that combines process characterization data with manufacturing operation control results. Previously, only end product testing was used to confirm quality of a product (*Quality by testing*), and such testing is not a part of manufacturing consistency or process control. The more proactive QbD approach begins by defining the desired clinical performance of a product; this establishes a quality target product profile. Then, product quality attributes necessary to achieve the quality target product profile are enumerated, and critical quality attributes are identified. During the recipe design stage, process steps that affect quality attributes are identified. The designed recipe contains critical and key process controls; e.g., reaction temperatures, compositions of process solutions, testing items, and test procedures. Process monitoring methods are also established to provide advance indications of potential failures. Process control is continuously improved by accumulating knowledge about product and process (Nasr, 2007; Lawrence, 2008). Setting in-process control parameters by a risk-based approach and controlling them by process analytical technologies has been called a close interpretation of QbD. But in the pharmaceutical industry, QbD substantially aims at cooperation among chemistry, manufacturing, and controls activities; hence, it is synonymous with LCE.

1.3 Toward Solving Problems on Lifecycle Engineering

Although both ICH Q8 and Q11 (ICH, 2012) describe the general concept of LCE and cite individual activities and outcomes, they do not explain overall business process management for product and process development. ICH Q10 (2008) focuses on business management, but it only covers management responsibility, product and process development flow, and an itemized list of required quality systems. Currently, business process management in pharmaceutical LCE is designed by contemplation of experts. For example, meeting committee structures, responsibility systems, and sets of required outcomes from LCE are set up and managed, on a case-by-case basis, by a limited number of experts. In other words, although a part of activities for LCE is put into practice, it is nothing but implicit management. This management approach, which extremely depends on personal efforts, generally does not succeed with rise number of products and development speed and

functional segmentation caused by enlargement of company size. Even though several years have passed since ICH Q10 was put into effect, the poverty of necessary information and lack of informational transactions still occur because of inefficient management of business processes; such situations have been documented in warning letters issued by the FDA from 2011 to 2013 (see: http://www.fda.gov/Drugs/default.htm). These warning letters were issued not only to small enterprises but also to mega–pharmaceutical corporations; this indicates that weaknesses in pharmaceutical management systems are industry-wide problem. For example, the warning letter (WL: 320-13-015) issued against Boehringer Ingelheim Pharma GMBH & Co on May 6, 2013 complained about lacking of investigation of a deviation. The firm did not conduct a thorough investigation to determine the source of foreign particles contaminated in active pharmaceutical ingredient of a product, nor did the firm implement timely and appropriate corrective and preventive actions. The firm's response acknowledged that while reports of the presence of the foreign particles were observed in batches produced in 2009, all of the batches in the campaigns beginning in 2008 should have been viewed as having comparable potential for contamination with extrinsic foreign particles. Based on the firm's response, there were several lots of active pharmaceutical ingredients manufactured in 2008 and the products manufactured in 2009 that had potential to be contaminated with foreign particles. Investigation found that 22 of the 29 foreign particle types were identified. Nonetheless, the firm decided to still use these contaminated lots to produce finished products. FDA were concerned that it was not until July 2012 that the firm began a formal project to implement comprehensive corrections to mitigate the presence of foreign particles in active pharmaceutical ingredients. In 2002, this firm installed the manufacturing execution system (MES) and deviation handling system relating with the MES (Werum, 2004). Although these systems work as instructing manufacturing operation procedures and recording manufacturing data and deviations, information handling process to achieve appropriate corrective and preventive actions was not supported. It is possible that the firm did not comprehend necessary business process. At least, there was no restricting function to control lot release before closure of related deviations. In addition, the document management system did not record the deviation to trace decision making process later. Hernad and Gaya (2013) explained methodology for implementing document management system to support quality management systems. They proposed six steps as, Step1: Definition of document requirements, Step 2: Evaluation of existing systems, Step 3: Identification of document management strategies in the organization, Step 4: Design the Document Management

System, Step 5: Implementation of the Document Management System, and Step 6: Maintenance and continuous improvement of the Document Management System. This methodology starts from current document and organization. However, desirable business processes has to be defined prior to design appropriate information transaction management system including documentation system. This business process may be managed by a limited number of experts if the information is handled within only small company. However, management on personal efforts does not succeed in functional segmentation caused by enlargement of company size. Normally, knowledge about engineering design processes is only known implicitly to the participating process designers, relying heavily on the personal experience background of each designer. To fully exploit this intellectual capital, it must be made explicit and shared among designers and across the enterprise (Brandt *et al.*, 2008). Van der Aalst *et al.* (2005) showed that traditional groupware products are data-driven (focus on the sharing of information rather than the process) and support only unstructured processes. Production workflows are process-aware and aim at structured processes. In order to enact a workflow using a production workflow system, it is needed to explicitly specify all possible business processes. Recent studies of computerized systems start to focus not only on recording data and information of manufacturing, R&D, and deviations but also on supporting business processes management.

Some studies emphasize the importance of management functions as conceptualized in the ICH Q10; however, they do not discuss practical management frameworks (Bringslimark and Warchut, 2008; Korakianiti and Rekkas, 2011; Cogdill and Drennen, 2008; Cardinal and Hatfield, 2000). Some pharmaceutical companies have recently adopted the term “quality culture” when they discuss management functions. Korakianiti and Rekkas (2011) have shown significant transitions in interpretations of quality (i.e., quality culture) from product focus to process and systems focus, since the former is an outcome that depends on the latter. The following key words suggest how quality has been regarded through the years: inspection, prevention, holistic and systems approach. The main pillars for these transitions were systems and knowledge theory, consideration of the involvement of all employees, psychology, and statistical tools for understanding variability and process monitoring. Bringslimark and Warchut (2008) explain that the management function does not have to do everything, nor does it have to involve the smartest people in an organization; however, management does have to create conditions under which other employees can achieve set goals. Management must always be asking questions like these: “What does the

company's quality culture look like?", "Is deviation management the business of quality assurance alone, or is it everyone's responsibility?" In summary, management must manage the quality culture of their company.

In 2007, the International Society for Pharmaceutical Engineering (ISPE) launched the Product Quality Lifecycle Implementation (PQLI) initiative (Garcia *et al*., 2008). The intention of PQLI is to work with industry and regulatory agencies worldwide to facilitate a common understanding of the quality by design approach; the initiative is also to introduce pragmatic and practical means to implement ICH Q8, Q9 (ICH, 2005), and Q10, based on solid scientific, engineering, and business principles. In 2008–2009, the PQLI initiative published a series of studies on the concept of LCE (Garcia *et al*., 2008), risk assessment (Nosal and Schults, 2008), outlines to determine the design space of a production process (Lepore and Spavins, 2008), engineering controls and an automation model based on ANSI/ISA S95 (Bolton and Tyler, 2008), process monitoring and control strategy (Davis *et al.*, 2008), and potential benefits from applying science and risk-based LCE (Potter, 2009). These studies also discussed the importance of the management function; however, no practical framework was presented. Schmitt (2011), Rathore and Mhatre (2009), and the CMC Biotech Working Group (2009) have summarized the train of pharmaceutical process development. While these studies are beneficial for identifying necessary activities, relationships between activities are not clear. During a pharmaceutical development and risk management process, significant amounts of information and data are generated. However, they have to be handled, managed, re-used and shared over the entire lifecycle of a drug product. ICH Q9 defines risk management as a "systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle." Currently, the typical results of a risk assessment/risk control process are paper-based documents or databases, i.e., the knowledge gained is captured in paper-based documents or stored in isolated databases (Guebitz *et al.*, 2012). Even though the electrical documentation management system is installed, it is just recording and searching system. As a result, the knowledge cannot be shared by various users of the product throughout its lifecycle. Communication and reuse (and to a certain extent re-generation) of the knowledge is therefore time-consuming and inefficient. Furthermore, the knowledge cannot be analyzed and updated, and as a result, a comparison with the experience gained later in the process is often extensive and error-prone. Thus, from a knowledge-management point of view, current risk management is data-rich yet knowledge-poor. Not only risk

information obtained in R&D but also that obtained in facility development and manufacturing have to be aggregated and used. What is needed is construction of a framework for comprehensive exchange of quality information among LCE activities (McKenzie, 2006).

In the current pharmaceutical process LCE, the major problem is that management, conceptualized in ICH Q10, cannot function appropriately because the management extremely depends on a limited number of experts. To solve this problem, we identify three broad steps: first, a comprehensive business process for pharmaceutical production process LCE needs to be developed to serve as a reference engineering activity model that can be used to analyze the current status of business process implementation. Modeling can generalize the business process which otherwise depends on the discretion of a limited number of experienced engineers. Second, then, we need to identify where the necessary information is created for the practice of LCE and where it should be used in the logical business process. The necessary information includes conditions, restrictions, outputs, and available information for each LCE activity. Appropriate protocols need to be prepared by integrating the information before the LCE implementation. Third, a framework must be designed that continuously improves the business process. Although one-way process development can be achieved based on some studies that show a train in pharmaceutical process development (Schmitt, 2011; Rathore and Mhatre, 2009; CMC Biotech Working Group, 2009), a framework for continuous improvement is required to realize the kind of lifecycle management, which ICH Q10 aspires. In many companies, including those in oil, petrochemical, chemicals, etc., engineering activity models have stimulated positive discussions on more logical ways for addressing safety and quality issues. Currently, the activity model-based approach is also expanding to pharmaceutical manufacturing (Naka, 2011). In pharmaceutical industries, a new paradigm is developing that supports LCE and uses logical activity models to reflect necessary business processes.

1.4 Thesis Objectives

In challenging cases explained in Section 1.1, industries and regulatory agencies have examined how to manage production process LCE. However, outcomes from those studies are still limited to individual methods and tools for specific objectives. A problem is solved through comprehensive efforts to assemble individual technical factors and human factors.

Effective management protocols that are often used to solve known problems can be systematized. These systematized protocols are used and improved if they are wrong. The systems approach is defined as systematizing patterned protocols and decision making processes performed by personnel into a framework and using it.

This study presents a systems approach for pharmaceutical production process LCE that manages necessary protocols on the basis of a logically illustrated business process in an activity model. A framework is proposed for covering change management in production process LCE. A supportive system is also presented for incorporating viewpoints from recipe scientists together with plant and process engineers.

The following studies are necessary to establish the framework.

- Illustration of the pharmaceutical production process LCE in a reference activity model.
- Identification of where the necessary information is created for the practice of LCE and where it should be used in the model.
- Clarification of the business process for change management to achieve continuous improvement of LCE activities.
- Determination of a process structure and design of supporting systems to develop production processes.

The benefits and novelty of this study are as follows: First, a lifecycle management framework, which is not explicitly discussed so far in any studies, is constructed. Second, the framework is used as the basis for continuous improvement of business processes. Third, the gap between recipe scientists and plant/process engineers is bridged and continuous PDCA cycle of production processes is achieved.

2 Necessity of Business Process Modeling

2.1 Introduction

Continuous improvement of product quality is accomplished by the exchange of information about products, processes, and operations. As explained in Section 1.3, conceptual guidelines for designing product quality into the production process have been known as the quality by design approach. Currently, the term *quality by design* tends to be used in a limited way to mean the development of a production process by risk-based design of experiments, rather than to refer to overall management of product and process development. *Lifecycle management* is simply used to mean overall management. The lifecycle management is necessary to avoid lack of informational interactions as documented in warning letters issued by the FDA in 2011 and 2012 (see: http://www.fda.gov/Drugs/default.htm).

Currently, the pharmaceutical industry cannot identify where the necessary information for LCE is created and where it should be used; the major reason for this seems to be the absence of an engineering activity model. To design quality into products and processes and to reduce development costs and time on the basis of both the latest scientific knowledge and accumulated past experience, it is essential to construct an engineering activity model for pharmaceutical product development. Gernaey and Gani (2010) have proposed a model-based framework focusing on a user interface. This framework bridges process and product models written in equations. Cervera-Padrell *et al*. (2012) applied the framework to continuous pharmaceutical production processes. This framework can find beneficial process information from accumulated R&D and production data. If the information found in the framework is disseminated and recorded appropriately on the engineering activity model, the value could be maximized.

In pharmaceutical industries, business process model has not been developed. In this chapter, we explain why describing a business process into an activity model is necessary to

implement LCE. Then we propose an appropriate structure for the engineering activity model prior to describing the business process of a pharmaceutical production process LCE. A logical framework to coordinate activities for business process management has been proposed.

2.2 Business Process Management Mediated by Activity Model

When industries start a business activity, first, an overall outline is made of business processes that will achieve business objectives (e.g., sequential paths of drug discovery, production process development, clinical studies, and application to a regulatory agency for launching a new drug into the market). Second, detailed business process is determined. Third, outputs from the business process are defined; these outputs may be compiled on a quality target product profile sheet and a process parameter risk assessment sheet. In addition, input items, constraints, and available resources are identified. For example, dosage form, targeting market size and region, and molecular geometry are defined as input items of the quality target product profile sheet. A risk assessment procedure is used to identify constraints that appear on the process parameter risk assessment sheet. The business process is implemented to complete the required outputs in sequence.

Currently, a business process in pharmaceutical LCE is designed based on a limited number of experienced engineers. A set of outputs for process development of a monoclonal antibody drug are introduced by a working group involving several biopharmaceutical companies (CMC Biotech Working Group, 2009). Although experts in this working group summarized the items needed to help biopharmaceutical industries create typical templates of outcomes, they did not explain the business process needed to manage process LCE. Because industries are still not be able to identify where the necessary information for LCE is created and where it should be used, they fail to smoothly bridge the process development stages in a process lifecycle. In addition, when a problem occurs in business process implementation, it is difficult to analyze root causes of the problem and excogitate corrective and preventive actions without the help of experts who are familiar with the backgrounds of the process development.

Figure 2-1 shows an overall outline of a pharmaceutical business process and the process development stages. Timelines for drug development and communication with a regulatory agency are placed within the fastest possible period, based on the business strategy,

target indication of the drug, and target market. Process development activities are roughly aggregated into four stages, whose duration and structure depend on objective product profiles. The early stage includes activities to produce the drug for preclinical study; these are based on product information that is obtained from drug discovery activities in the form of a quality target product profile and critical quality attributes. In this early stage, items of product quality attributes can be determined, but the quality range of the attributes and required productivity may not be clearly determined because no information is available from pre-clinical and early clinical studies. In general, pharmaceutical product quality is not determined by customer demand but by results from pre-clinical and clinical studies and oversight of regulators (Cogdill and Drennen, 2008). Since proof of concept for a drug can only be assessed during or after early clinical studies, a detailed commercial production plan may not be possible before completing clinical studies. For example, a quality target product profile may be changed based on early clinical results (e.g., a change in the form of dosage from liquid to lyophile; addition of children to the target age). It is a specific characteristic of the pharmaceutical industry that requirements on product quality, productivity, and commercialization cannot be clearly decided during the first process development stage.

In the middle stage, the recipe and facility are developed, and drug samples for early clinical phases are produced based on the developing recipe and facility. During this stage, product quality requirements and the commercial production scale are determined. In the late stage, the commercial recipe is finalized and characterized. Based on results from process characterization studies and past manufacturing information, process performance is qualified in a commercial plant. After approval, the process will be maintained by continued process validation activities during the continued stage. A process is developed through this process lifecycle. In this situation, the production process LCE is implemented by iterative process improvement from an early stage rather than in a single path development. Some outcomes, shown in black boxes with white characters in Figure 2-1, are produced at the early stage and modified as the process LCE stages progress. In particular, recipe transfer materials, including process master recipe, production control chart, and sampling list have an important roles in integrating information produced by recipe design, facility design, and production activities. To implement business process based on this overall outline, industries have to identify where the necessary information and outcomes for LCE are created and where they should be used.

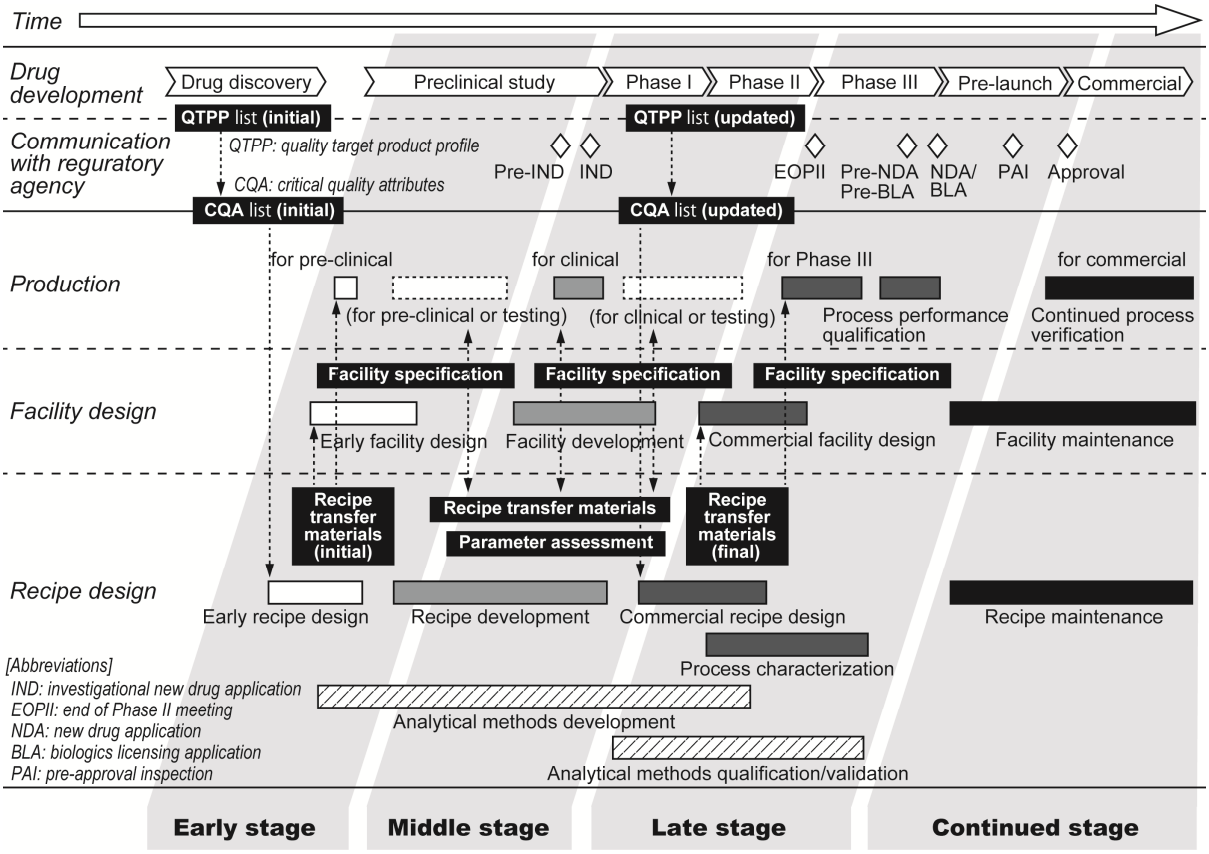


Figure 2-1 Overall outline of a business process on pharmaceutical process development. Upper two rows indicate drug development and communication points with regulatory agency. Lower three rows indicate process development activities. Black boxes with white characters are parts of outcomes produced in pharmaceutical business activities. Process development in pharmaceutical lifecycle is divided into four stages, as shown by gray zones. Color strength of major activities in recipe design, facility design, and production are darkened as the stages progress.

In Figure 2-2, we propose that business process management be mediated by an activity model. In this scheme, first, objectives of a business and overall outline of the business activities are determined. The reference activity model is then constructed by using a modeling template. Current business systems, protocols, and organization structure would be helpful to make an initial picture of the model. Business process is then analyzed based on the reference activity model. Without the reference activity model, business process management depends on personal contemplation. However, it is impossible to comprehend overall business process and manage it by a limited number of experts. To review and improve business process that has been supported by experiences of the experts, the business process has to be cast into a reference activity model. A set of outputs, associated input items, constraints, and available resources are defined on the reference model. Individual protocols

and systems are then designed and deployed. The systems here mean educational systems and organizational structure as well as procedures, engineering standards, and computerized applications. Implementation of business processes are supported by these protocols and systems. If a problem occurs, business process review can trigger improvement of transaction methods and/or transaction schemes. The individual protocols and systems are built in the reference model. Business processes are performed by tracing the protocols. If defects are found on a protocol, the contents of it are redesigned. This is improvement of transaction methods. On the other hand, if a business process does not work well due to lacking in definition of necessary activities on the model, the activities are newly defined and relating protocols and systems are designed. This is improvement of transaction schemes. Activity model-based approach manages business process by these improvements of transaction methods and schemes.

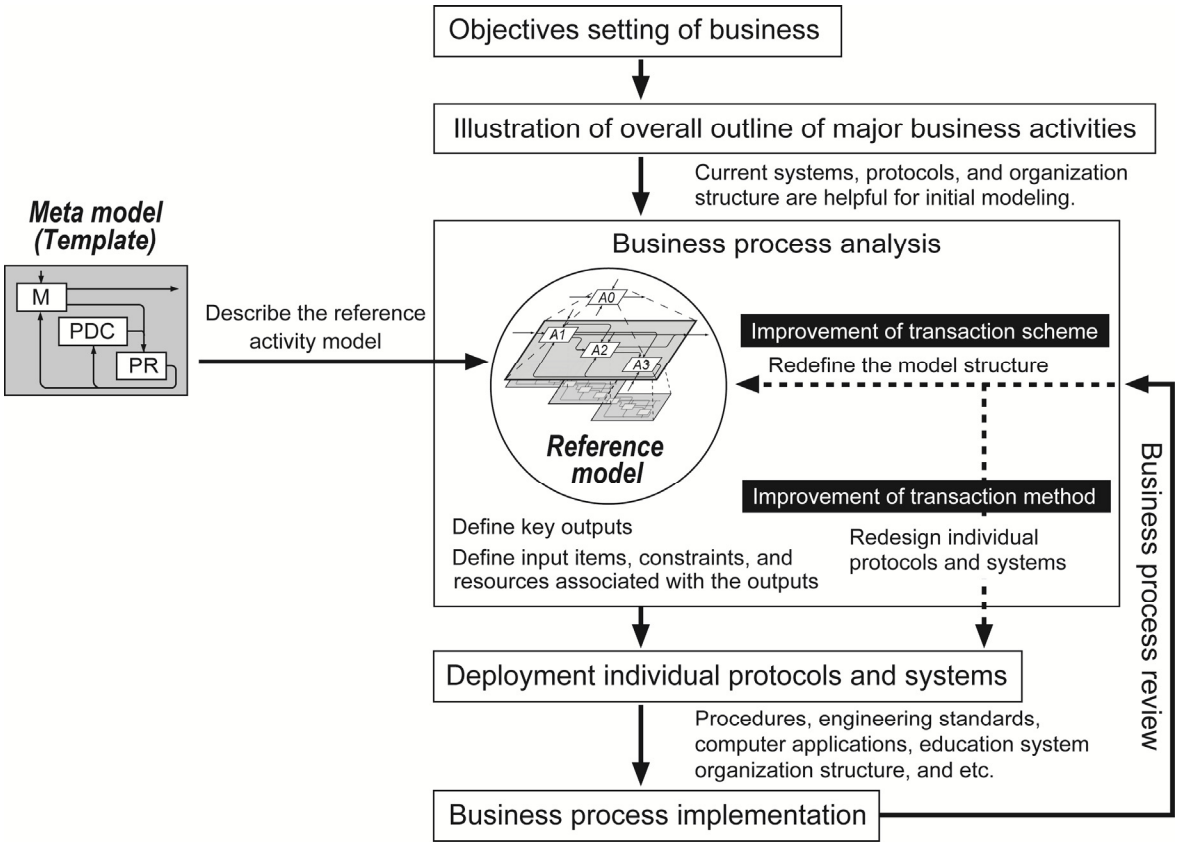


Figure 2-2 Activity model-based business process management.

In this framework, Plan-Do-Check-Act (PDCA) is performed as part of business process management. Business process analysis on the activity model corresponds to the Plan

step in the PDCA. For business process analysis, it is necessary to aggregate information on different timelines and organizations. The type-zero method of integrated definition language (IDEF0) (NIST, 1993) is a function modeling methodology to describe business process into a static model. The model written in IDEF0 represents functions of a business and separates organizational viewpoints from the model. The model also results in an organized representation of the functional activities and the important relations between these activities in a non-temporal fashion. Relations between the activities are defined with a set of outputs, associated input items, constraints, and available resources. A detailed business process can be described in an IDEF0 model to identify the structure of information transactions. Sugiyama and Schmidt (2012 and 2013) have studied the design responsibility systems in the so-called RACI (responsible, accountable, consulted, and informed) model on the basis of a business process model. Business process analysis on the basis of an activity model supports management functions that build, monitor, analyze, judge, and improve personnel factors (e.g., personal cooperation, personnel training systems, committee structures, and responsibility systems) as well as technical factors (e.g., technologies, procedures, infrastructures, and other supporting tools for propelling activities).

The model is required to include the PDCA function performed among overall activities. Clear PDCA function represents improvement scheme of a production process from early to late lifecycle stages as shown in Figure 2-1. The business process in the model has to indicate a dissemination scheme for information on a current problem, results from causal investigations, proposals for improvement, risks associated with changes, and implementation. In the next section, we propose a template for an IDEF0 activity model to satisfy this requirement.

2.3 Model Structure

2.3.1 IDEF0

IDEF0 is used to model pharmaceutical lifecycle process engineering. IDEF0 was originally developed as a function modeling method for analyzing and communicating system function flows by the United States Air Force and finally by the National Institute of Standards and Technology (NIST, 1993). IDEF0 activity modeling has been applied to describe the engineering systems for recipe design and manufacturing in such industries as

mechanical engineering (Barkmeyer, 1996), safety engineering (Fuchino and Shimada, 2003; Fuchino *et al.*, 2007), and chemicals (Sugiyama *et al.,* 2006). In modeling by IDEF0, the information necessary to perform an activity is categorized into four types; Input, Output, Control, and Mechanism, together abbreviated as ICOM. As shown in Figure 2-3, an activity is described as a verb in a rectangle box with Input arrows into the left side of the box and Output arrows from right side of the box. The Input information is converted into Output under constraint represented by the Controls (arrows into the top of the box) such as directives and standards. The conversion is facilitated or supported by the Mechanisms (arrows into the bottom of the box) such as available resources and information. An activity must have at least one output, but inputs, controls, and mechanisms are applied if necessary. An activity may be decomposed into more detailed sub-activities and connected by ICOMs so as to organize the activities' hierarchy, describing both the horizontal and vertical information transaction. The IDEF0 activity model clarifies the boundary (or the range) of the information handled by the process.

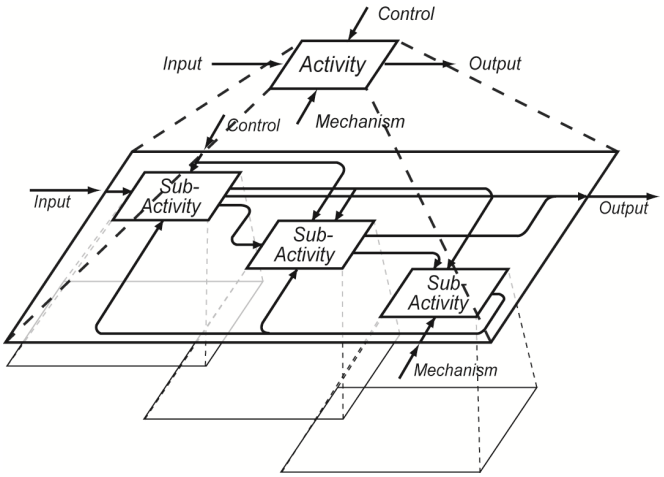


Figure 2-3 Properties of the IDEF0 activity model.

2.3.2 Model Template

Although IDEF0 provides a standard description format, model structure consistency depends on individuals' application of the format. Making a template is useful to improve the IDEF0 activity model's consistency. In addition, PDCA function which is to be performed ubiquitously in the activities in the process lifecycle engineering stages in Figure 2-1 has to be defined in the template. The international process industry group, PIEBASE (Process Industry Executive for achieving Business Advantage using Standard for data Exchange), proposed an activity model template describing enterprise activities of the process industry (Fuchino *et al.,* 2011). The PIEBASE modeling template has been applied to describe the

lifecycle engineering system in the chemicals industry (Fuchino *et al.,* 2007) and safety engineering (Fuchino *et al.,* 2008). The template was modified by the Process Safety Management working group of the Society of Chemical Engineers, Japan (Fuchino *et al.,* 2010; Shimada *et al.,* 2010).

We referred to this modified template and developed the pharmaceutical activity model template through preliminary modeling of pharmaceutical process LCE. The template is as Figure 2-4–Figure 2-7. In this template, an Execute activity consists of the sequential activities of Manage, Plan, Execute, Evaluate, and Provide resources. It enables the detailed description of the PDCA cycle occurring in an activity layer. Plan, Do and Check are reflected in Plan, Execute, and Evaluate activities, respectively, and Manage draws a final decision (Act) from the results of Plan, Execute, and Evaluate activities. The PDCA occurring among the same layer's manage, plan, execute, evaluate, and Provide resources activities is defined as *horizontal PDCA*. The final decision completes the continuous improvement cycle by establishing new propositions, controlling activities' progression, reallocating resources, and loosening or tightening internal technical standards. The *Act* in the PDCA corresponds to management function of judgment (or certification), set propositions, and change requests to given restriction. The results generated through the PDCA are summarized in the Provide resources to serve not only the same layer's activities but also the activities of the upper and lower layers as required. The Provide resources activity aggregates served information and provides risk information as action proposal. The definition of PDCA cycle lacks function of the Provide resources, that is recording, aggregating, and providing information. Based on this study's template, the PDCA should be expressed as MPDC-PR (Manage-Plan-Do-Check and Provide resources), but, commonly accepted expression, PDCA, is used in this thesis.

Essential process on the template can be divided into A: Setting proposition and planning (Figure 2-4), B: Applying regulations, guidelines, and standards (Figure 2-5), C: Handling of execution results and risk information (Figure 2-6), and D: Providing and requesting resources (Figure 2-7). Although these four figures' structure is the same, the essential business process for each object is highlighted by bold lines and labels. A Manage activity establishes a proposition to be handled within the layer. The proposition is determined based on change proposals generated by the current layer's activities as well as directives, plans, and requirements provided by the upper layer. An appropriate solution to the proposition evolves through PDCA cycles. A Plan activity provides a detailed execution

plan to execute and evaluate phases based on the directives provided by the Manage activity. The regulations, guidelines, and standards provided by the upper layer are expressed as internal engineering standards and procedures (Figure 2-5), which operate as restrictive conditions for activities' execution. The summary of execution results, which is generated per the detailed execution plan, is provided to Evaluate and Provide resources activities (Figure 2-6 dash-dotted line). The comprehensive summary of all results obtained in the activity layer is provided to the Evaluate and Provide resources activities on the upper layer through the Manage and Provide resources. Risk information is distinguished from the execution results in the model template, because they are particularly important in pharmaceuticals quality management (Figure 2-6 solid line). Prospective risk assessment is conducted in the Plan activity. The risk assessment result is provided to the Evaluate and the Provide resources activities. The Execute activity provides the risk management summary to the Evaluate and Provide resources activities, and this summary is generated by a series of activities on the lower layer of the Execute activity. The Evaluate activity reviews the risk assessment result from the Plan activity and the risk management summary from the Execute activity as well as the summary of execution results. The risk review summary is provided to the Provide resources activity. The Provide resources activity summarizes the risk management information of the current layer from its risk assessment summary and risk review summary, and lower layers' risk management summaries. The risk management summary is provided to the upper layer's Evaluate and Provide resources activities. Necessary information for risk evaluation and PDCA execution such as past risk management information, past development results, external information, academic information, and related information from other layers is provided by the Provide resources activity (Figure 2-7). This information is provided per information requests generated from each activity. In current industries, risk assessment may be performed one-time-only to prepare deliverables to regulatory agencies. The assessment documents are held in a limited group and unused as living documents. Risk assessment can be performed in a limited group exclusively and trigger arbitrary changes unexpected by other groups. Function of Provide resources is separated from Manage, Plan, Execute, and Evaluate functions. The separated Provide resources function is important to avoid the exclusive possession of risk information and occurrence of arbitrary changes based on narrow scope risk assessment.

Business activities are ideally executed by only horizontal PDCA cycles. In reality, however, they experience problems because propositions, constraints, plans, and standards

provided from upper layers are sometimes inappropriate or unachievable. Therefore, the model template describes a system which aims to improve transactions between layers. If the execution plan contains risk, a change proposal to the plan is output as shown in Figure 2-4. If internal engineering standards need to be modified due to business restructuring or a new regulatory concept such as computerized validation, then each activity outputs change proposals for internal engineering standards to the Provide resources activity. The Manage activity determines whether the change proposals are reasonable and outputs them to the upper layer should a solution be feasible from constraint relaxation (Figure 2-5). Consequently, appropriate new plans and internal engineering standards can be developed. The Provide resources activity requests information resources from the upper layer if needed (Figure 2-7). This PDCA process between the layers is defined as *vertical PDCA*.

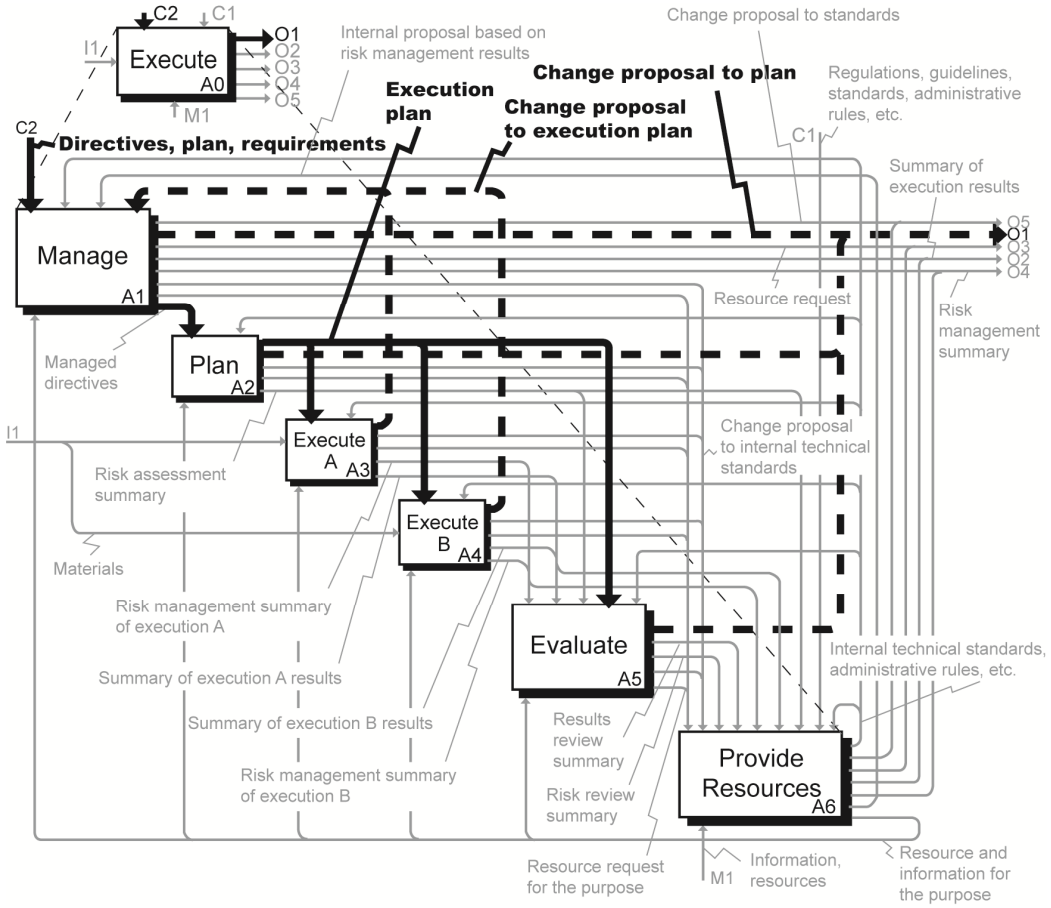


Figure 2-4 Template of activity model highlighted process on setting proposition and planning.

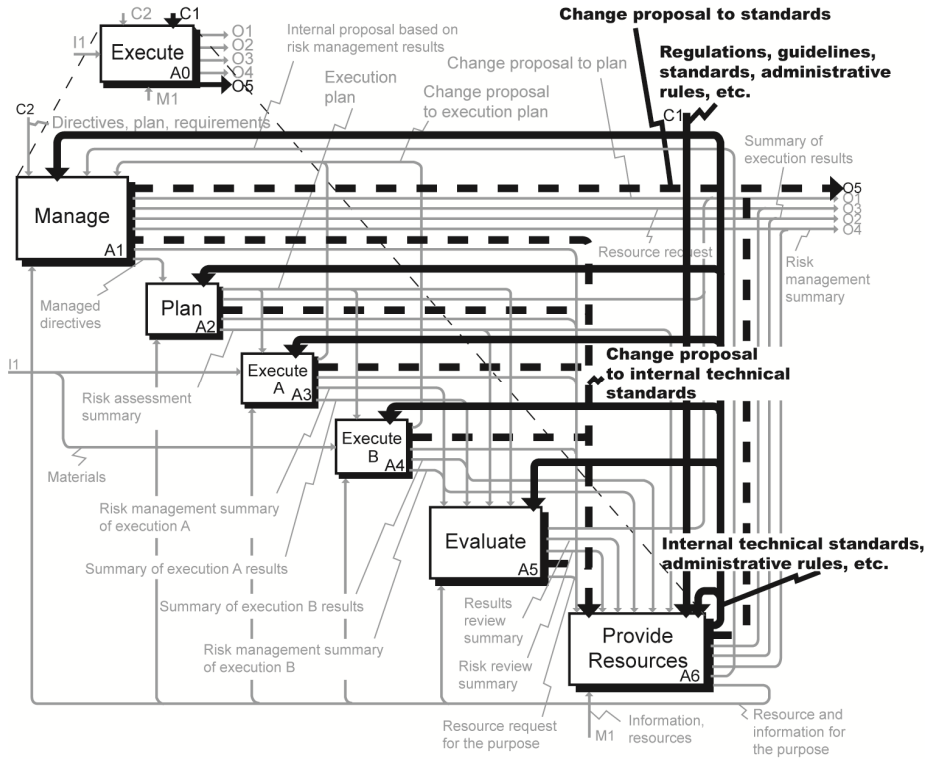


Figure 2-5 Template of activity model highlighted process on applying regulations, guidelines, and standards.

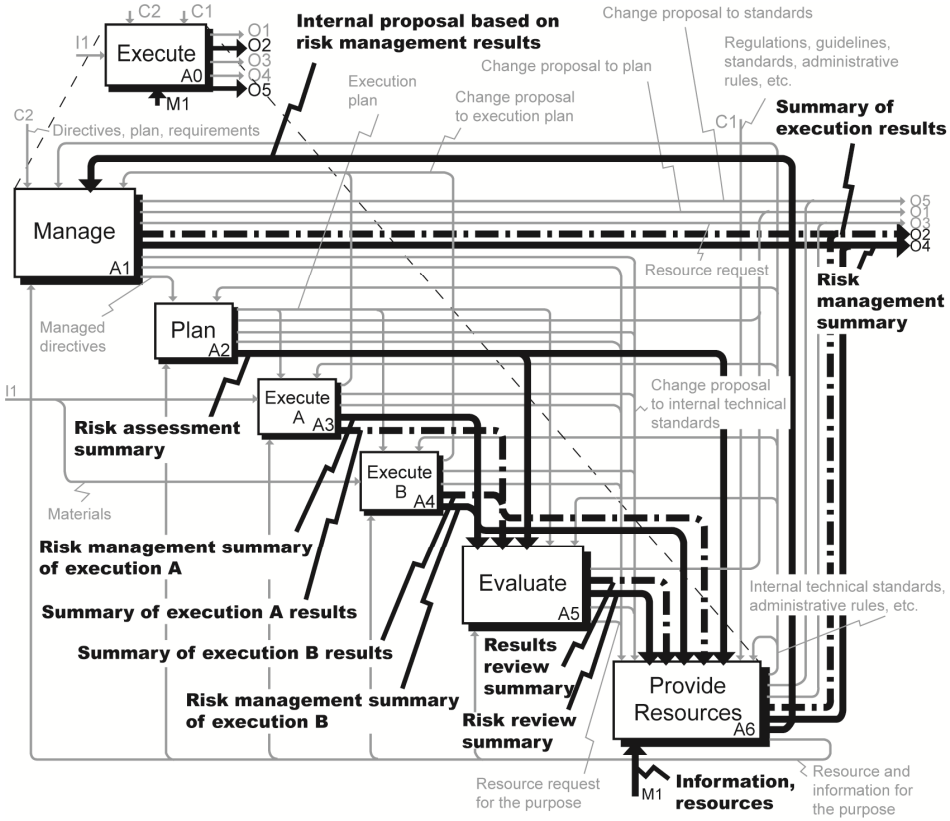


Figure 2-6 Template of activity model highlighted process on handling of execution results and risk information.

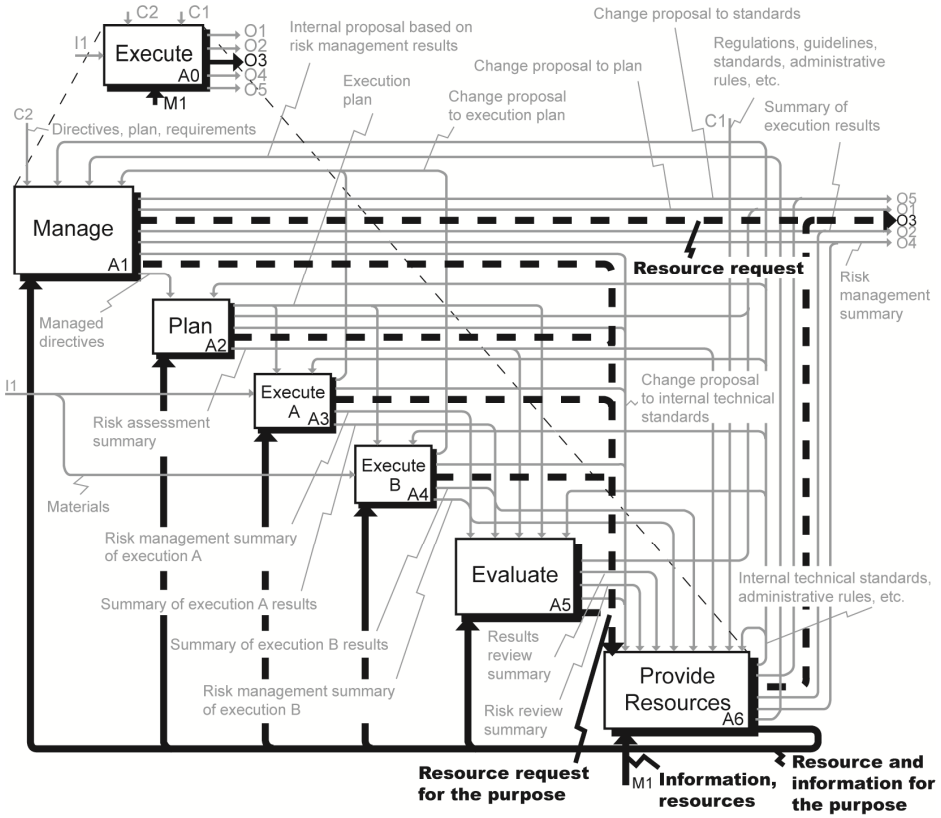


Figure 2-7 Template of activity model highlighted process on providing and requesting resources.

2.3.3 Structure to Achieve Overall PDCA

The model template defines the horizontal and vertical PDCA occurring among overall activities. The schematic structure of the model is shown in Figure 2-8. Horizontal PDCA is defined as Manage, Plan, several Executes, and Evaluate activities on a layer (black-back and gray-back boxes). Vertical PDCA is defined by the plan served on an upper layer, several Execute activities on lower layers, Check activities on lower layers, and change proposals against the served plan from the Manage activity on the lower layer. The Provide resources activity gathers development results (plan, execute, and evaluate results) and serves summarized risk information. This risk information is used as action proposal for the Manage activity. On the basis of this information, the Manage activity decides commencement of appropriate actions. The Provide resources activity outputs internal improvement proposals to the same layer in order to minimize current risk based on the summarized risk management information (Horizontal improvement). In addition, the risk management summary provided to the upper layer contributes to the upper layer's improvement proposals (Vertical improvement). The Provide resources activity that expands the gathered information to all dimensions facilitates both local and fundamental, system-wide improvements.

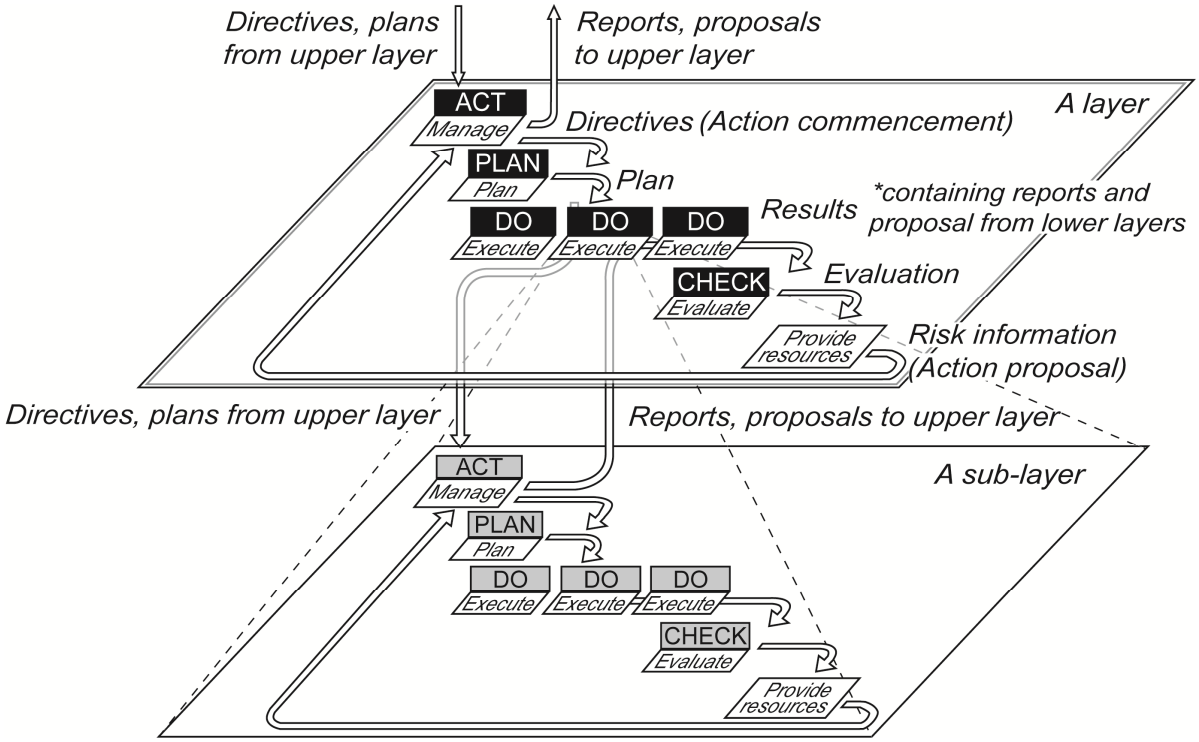


Figure 2-8 Horizontal and vertical PDCA occurred in the activity model.

2.4 Conclusions

In this chapter, we drew an overall outline of pharmaceutical production process LCE. Although the outline showed major activities and outcomes, it is not identified where the necessary information for LCE is created and where it should be used. A detailed business process has to be described in a model so we can identify the structure of information transactions. We use the IDEF0 to aggregate information in different timelines and organizations and to describe a static function model that clarifies relationships among activities via a set of outputs, associated input items, constraints, and available resources. In the pharmaceutical industries, production process LCE is implemented by iterative process improvement from an early stage rather than in single path development. To manage this iterative process for improvement, it is required to manage PDCA cycles which occur among overall activities. We prepared a modeling template to define not only the horizontal PDCA cycle on a single activity layer but also the vertical PDCA cycle between activity layers.

Without the reference activity model, it is impossible to manage business process depends on only personal contemplation. To review and improve a business process, the business process has to be cast into a reference activity model. The activity model-based

logical framework to clarify a business process is needed to coordinate activities and outcomes, which are otherwise left unstructured and unrelated in current industries. In pharmaceutical industries, business process model has not been developed. In the next chapter, we propose methodology and the template to build the pharmaceutical process LCE model, and we illustrate the business process structure as it is defined on that model.

3 Framework to Manage Business Process

3.1 Introduction

To find an appropriate business process for a given purpose, all activities and relationships must first be identified. An information sharing system can be designed by analyzing relationships of the activities. To design a framework to manage pharmaceutical process LCE, pharmaceutical development and production engineering activities must be arranged. The major engineering stages are defined as shown in Figure 3-1, based on Nasr's QbD diagram (Nasr, 2007). In Figure 3-1, the circular arrows indicate LCE activity stages, and rectangular items are major outputs produced by those stages. The stages are separated into product and process engineering by the gray diagonal arrow.

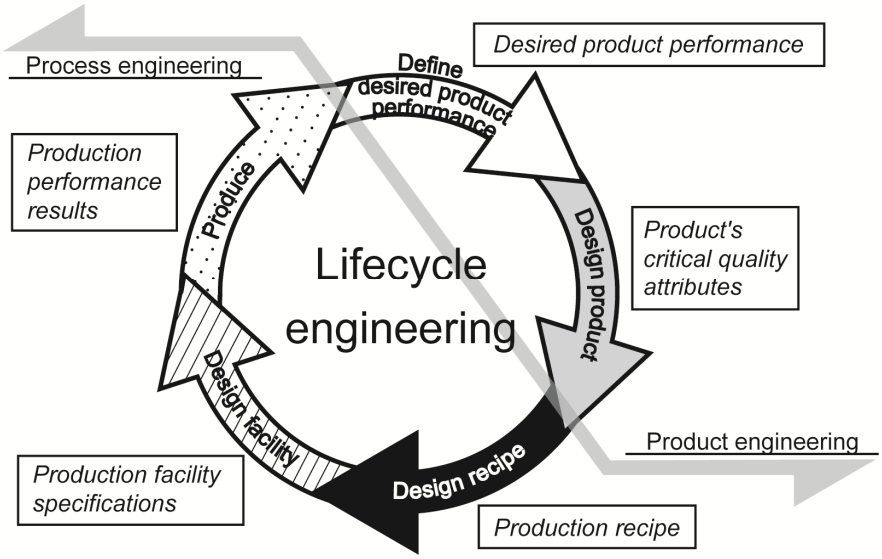


Figure 3-1 Major stages in lifecycle engineering based on Quality by Design approach.

LCE is divided into five activity stages: Define desired product performance, Design product, Design recipe, Design facility, and Produce. Drug discovery, pre-clinical study, and clinical study functions are involved in the Define desired product performance stage.

Because this study focuses on process engineering, detailed modeling is limited to the stages except for the Define desired product performance stage. Here the recipe refers to information on raw materials, their relative quantities, and required processing conditions. In design facility stage, the facility describes analytical instruments and R&D facilities as well as plants, equipment, and devices for pharmaceutical production. The Design facility stage is explicitly defined in this study because of its importance in process engineering, although only an implicit focus is put on this activity in previous studies on pharmaceutical process LCE. In preparing to produce pharmaceuticals, production facilities are designed or modified, the design feasibility for production is tested, and detailed control procedures are determined. Production operations are controlled by the procedures specified for the production facilities.

The simple circular diagram in Figure 3-1 does not describe the practical business process adequately. In current pharmaceutical industries, a limited number of experts still determine the business process and related procedures such as committee structures, responsibility systems, and outcomes. This approach of management, which depends on personal efforts, is no longer capable of coping with the situation that the number of products and development speed increase. In this chapter, we illustrate the business process of pharmaceutical process LCE in an activity model by using the template explained in Section 2.3. We also explain activity model-based management for implementing LCE.

3.2 Coordination of Process Lifecycle Engineering Activities

3.2.1 Introduction

The management depending on personal efforts needs to be generalized for continuous improvement of business process. In this section, the business process to implement the activities defined in Figure 3-1 is logically illustrated in an activity model by using template explained in section 2.3. The activity stages are divided into process and product engineering. Because the engineering activities for developing processes and designing products are intricately intertwined, it is important for LCE implementation to understand the relationship between these two types of activities. We propose a to-be activity structure for integrating the LCE activities appropriately.

3.2.2 Developed Model

The activity model describing pharmaceutical production process LCE was created by using the modeling template. Figure 3-2 shows the node tree of a section of the entire model. The top layer's activity; "A0: Execute process LCE for pharmaceuticals," is decomposed into seven activities on the second layer: "A1: Manage execution of LCE," "A2: Plan execution of LCE," "A3: Develop production recipe," "A4: Develop production facility," "A5: Produce pharmaceuticals," "A6: Evaluate execution of LCE," and "A7: Provide resources for LCE." The second layer is shown in Figure 3-3. As for the third layers, structures of activities A3, A4, and A5 are similar to those of the second layer. Structures of activities A1, A2, A6, and A7 are shown in Appendix-A. Structures of Manage, Plan, Evaluate, and Provide resources are similar to the activities A1, A2, A6, and A7, respectively. The activities are detailed on the lower layers such as "A3434: Develop recipe of culture expansion process" and "A3435: Develop recipe of main cultivation process," which are decomposed from "A3: Develop production recipe." The activity A0 is on the top layer and coordinates the all-embracing policies for business decision making. In practice, the first layer would be a part of a layer including "Execute discovery research targeting new pharmaceutical development" and "Execute preclinical and clinical development of pharmaceutical candidates." The desired product performance is defined from information obtained by discovery research and clinical development activities. In the second layer, a series of engineering activities for the product development projects are coordinated. In the third layer and lower layers, the activity is detailed to implement LCE. The Manage and Provide resources activities of all layers are related so that the development results and risk management information are exchanged comprehensively among the all activities. For example, "quality risk information for pH in a purification process operation," which is obtained in a lower activity of "A3: Develop production recipe," is recorded in "A7: Provide resources for LCE" via the Provide resources activities of lower layers. Then, this information is provided to the Provide resources activities on the lower layers of "A4: Develop production facility" and "A5: Produce pharmaceuticals." In activities A4 and A5, this information triggers improvements such as remodeling purification equipment and changing instructions in standard operating procedures.

A series of information warehoused in the Provide resources activity is available for future activities execution. Risk information warehoused hierarchically as described above enables reasonable and meaningful risk management by integrating the risk information of

different layers, unlike conventional risk management systems used for limited objects and with makeshift documentation. It is necessary that all development activities are managed by the engineering activity model in order to carry out essential risk management and to reflect the risk information in the quality design. In current industries, risk assessment seems to be performed from viewpoints of recipe design. In this model, risk management is defined in both “A4: Develop production facility” and “A5: Produce pharmaceuticals” as shown in Figure 3-3. The comprehensive risk information from the viewpoints of not only recipe design but also facility design and production is aggregated in the Provide resources and fed back as needed. The separated Provide resources function is important to avoid the exclusive possession of risk information and occurrence of arbitrary changes based on narrow scope assessment.

- A0: Execute process LCE for pharmaceuticals
  - A1: Manage execution of LCE
    - A11: Manage output of directives and proposal concerning LCE
    - A12: Output directives to implement business plan with appropriate risk and benefit
    - A13: Output proposal provided from A2-7 after judgment
    - A14: Output the results and reports provided from A2-7 after judgment
  - A2: Plan execution of LCE
    - A21: Manage planning of LCE execution
    - A22: Organize business demand such as quality target product profile, critical quality attributes, market profile, required yield, and deadline (Object setup)
    - A23: Organize resource conditions such as available facilities' production performances, achievable yield and development speed (Constraint setup)
    - A24: Create the LCE execution plan based on the organized conditions
    - A25: Assess the risk of the execution plan
  - A3: Develop production recipe
    - A31: Manage development of production recipe
    - A32: Plan development of production recipe
    - A33: Prepare for recipe development
    - A34: Develop cell line
    - A35: Develop recipe of drug substances and drug products (DS/DP) manufacturing process
      - A351: Manage development of recipe of DS/DP manufacturing process
      - A352: Plan development of recipe of DS/DP manufacturing process
      - A353: Develop recipe of upstream process
        - A3531: Manage development of recipe of upstream process
        - A3532: Plan development of recipe of upstream process
        - A3533: Develop recipe of cell banking process
        - A3534: Develop recipe of culture expansion process
        - A3535: Develop recipe of main cultivation process
        - A3536: Develop recipe of cell removal process
        - A3537: Evaluate development of recipe of upstream process
        - A3538: Provide resources for development of recipe of upstream process
      - A354: Develop recipe of downstream process
      - A355: Develop formulation and filling vessel and package of DS/DP
      - A356: Develop recipe of formulating and packaging process
      - A357: Evaluate development of recipe of DS/DP manufacturing process
      - A358: Provide resources for development of recipe of DS/DP manufacturing process

Figure 3-2 Node tree of the proposed engineering activity model of pharmaceutical LCE.

- ≈ ≈
  - A36: Develop analytical methods
    - A361: Manage development of analytical methods
    - A362: Plan development of analytical methods
    - A363: Select suitable methods and instruments
    - A364: Adjust selected methods
    - A365: Determine procedures from adjusted methods
    - A366: Transfer the procedures
    - A367: Evaluate development of analytical methods
    - A368: Provide resources for development of analytical methods
  - A37: Evaluate development of production recipe
  - A38: Provide resources for development of production recipe
- A4: Develop production facility
  - A41: Manage development of production facility
  - A42: Plan development of production facility
  - A43: Prepare for production facility development
  - A44: Design production facility
  - A45: Construct and install production facility
  - A46: Test the production facility
  - A47: Evaluate development of production facility
  - A48: Provide resources for development of production facility
- A5: Produce pharmaceuticals
  - A51: Manage production
  - A52: Plan production
  - A53: Prepare for manufacturing and maintenance
  - A54: Manufacture pharmaceuticals
  - A55: Maintain production facility and laboratories
  - A56: Evaluate production
  - A57: Provide resources for production
- A6: Evaluate execution of LCE
  - A61: Manage evaluation of LCE execution
  - A62: Evaluate the results are according to plan
  - A63: Reassess the risk of the execution plan
  - A64: Evaluate overall LCE management process
- A7: Provide resources for LCE
  - A71: Manage providing information and resources for LCE
  - A72: Aggregate information about risk management of LCE and provide it as improvement proposal
  - A73: Aggregate implementation results of LCE and provide it as knowledge
  - A74: Aggregate information about LCE project management and provide it as knowledge
  - A75: Aggregate information about regulations and internal rules and provide it as LCE procedures

Figure 3.2 (continued)

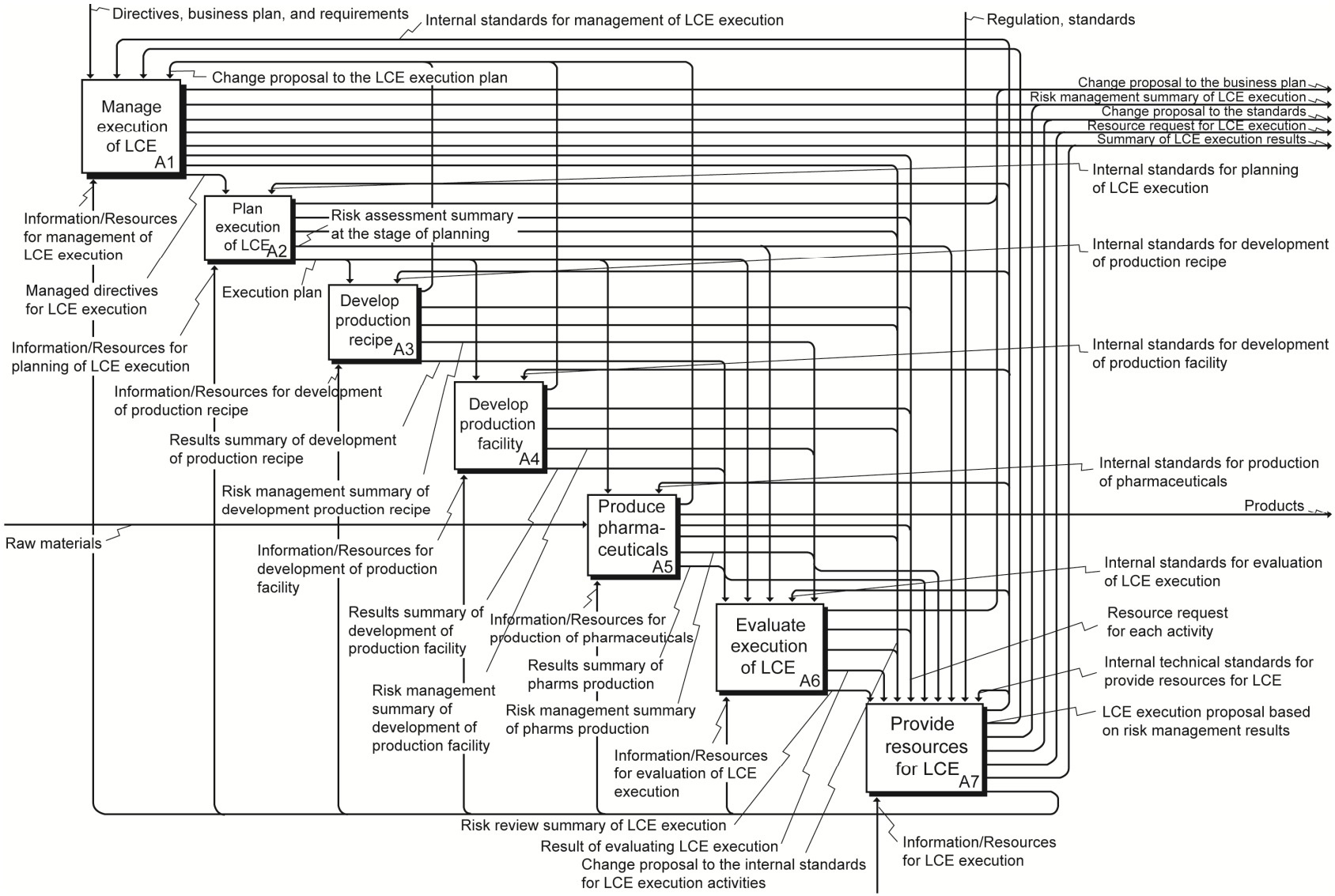


Figure 3-3 The second layer of the LCE model.

3.2.3 Structure of Business Process for LCE

The diagram in Figure 3-4 illustrates how the five LCE activity stages shown in Figure 3-1 are related to the engineering activity model. The information related to the activity stages (Define desired product performance stage, Design product stage, Design recipe stage, Design facility stage, and Produce stage) are represented in the engineering activity model by white, gray, black, dotted-dashed, and dashed lines, respectively. The major information exchanged beyond the stages is represented by the black-white head arrows and the gray boxes. These activity stages are coordinated by exchanging directives, constraints, change proposals, standards, and risk information, as well as the information in gray boxes.

Thus, the LCE activity stages functionally interrelate in the hierarchical structure of business process. The hierarchy consists of first the Define desired product performance stage, second the Design product stage, and third the three subordinate stages: Design recipe, Design facility, and Produce. Function of the second stage is not only product design but also business process coordination for quality design. The activity A0 of this model belongs to the Define desired product performance stage. The seven sub-activities of A0 (i.e., A1, A2, A3, A4, A5, A6, and A7) belong to the Design product stage. The three implementation stages, Design recipe, Design facility, and Produce correspond to sub-activities of A3, A4, and A5, respectively. The desired product performance (i.e. quality target product profile shown in Figure 2-1) is defined and provided from the Define desired product performance stage to the Design product stage. The critical quality attributes are determined and warehoused in the Design product stage. The developed (or developing) recipe is fed back to the Design product stage. The recipe information and production plan are provided to activities A4 (Design facility stage) and A5 (Produce stage). All information outputs of engineering and production containing recipe development results, production facilities information, process control operation procedures, and production results are fed back to the Define desired product performance stage via the Design product stage. Product and process engineering information are consolidated in the Provide resources of the Design product stage. The information warehoused in the Provide resources activity contains the background and rationale for determining critical quality attributes, recipe development history, production facilities specifications, products' quality specifications, analytical results of products, production incident summaries, and the like. All Provide resources activities, especially those of the Design product stage, are informed by horizontal and vertical know-how feedback through a

number of product development iterations, and thus contribute to the continuous improvement of the quality design rationale.

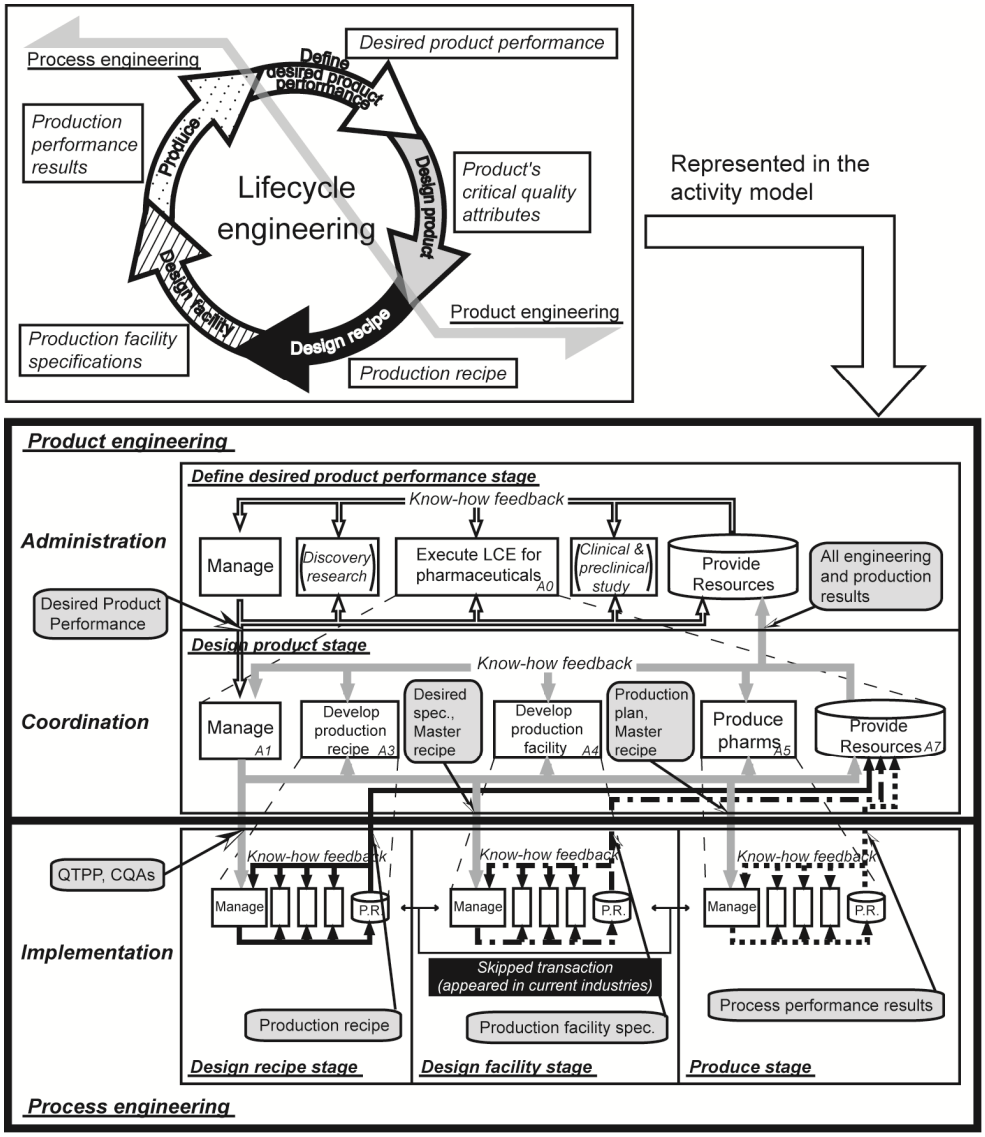


Figure 3-4 The coordination scheme of the five LCE activity stages. Pharms: pharmaceuticals, P.R.: Provide resources, Spec.: Specification.

The business process of LCE illustrated on the engineering activity model shows how LCE is accomplished, not by the simple circular sequential alignment of the five activities shown in Figure 3-1, but by horizontal and vertical PDCA which occur in the five activities arranged as shown in Figure 3-4. The Design recipe stage, Design facility stage, and Produce stage are chronologically sequential activity stages, which correspond to the sequential execution of a pharmaceutical development project in early, middle, and late stages of process LCE in Figure 2-1. The three stages are connected in parallel with the Design product

stage from the perspective of business process and storage to inform future continuous improvement. The information from the Produce stage is not fed back directly to the Define desired product performance stage but via the Manage and the Provide resources activities in the Design product stage. The Design product stage bridges process and product engineering. Process engineering, realized by coordination of the Design recipe, Design facility, and Produce stages, is facilitated by information management in the Design product stage. Process engineering information is leveraged by the Design product stage for product engineering, realized by coordination of the Define desired product performance and Design product stages. This LCE business process designed on the engineering activity model enables each pharmaceutical LCE activity to recognize the communication target and the information warehouse location for its activity execution.

In the current industrial settings, the three activities, the Design recipe, Design facility, and Produce, may be executed without going through the upper layer Design product stage. This skipped transaction is expressed by thin arrows and black box with white letter in Figure 3-4. Although the skipped transaction may have the benefit of transferring information quickly, it is also necessary to transfer the information to the Design product stage in order to achieve continuous quality improvement. For example, if "information of quality risk related to pH controlled in a purification process" is transferred from the activity A3: Develop production recipe to the activity A5: Produce pharmaceuticals directly without transfer to the A7: Provide resources for LCE activity as well, temporal manufacturing can proceed without any problem. However, in the case of new facility construction or facility remodeling for the purification process, the A4: Develop production facility activity would design the purification equipment that controls the pH inappropriately or create an insufficient pH control test plan for the purification equipment, because the information about the pH quality risk has been neither warehoused in the activity A7: Provide resources for LCE activity nor provided to the activity A4: Develop production facility. It has been observed that quality information is lost in industrial settings where projects are executed by skipped transaction without warehousing the communicated information for the Design product stage. Constrained by the circular diagram in Figure 3-1, industries tend to lapse into such a situation. The skipped transactions appear in current industries, but they are eliminated in the engineering activity model, because they would result in an improper business process. Note that the business process written in the model does not describe an organizational structure. Denying business process implemented by the skipped transaction does not mean that direct

communication between a recipe researcher and a process engineer is prohibited. What is important is that a system to facilitate and record communication is present. A person who has information to be shared is obliged to communicate with another person only through the second layer of the model. Such a system cannot be built without the business process model. A management system built on the basis of the activity model in this section is explained in the next section.

3.2.4 Summary

In this section, pharmaceutical process LCE was unambiguously arranged into five activity stages by the IDEF0 engineering activity model. This model frames the hierarchical activities of first the Define desired product performance stage, second the Design product stage, and third the three subordinate stages: Design recipe, Design facility, and Produce. This hierarchical structure represents function of administration, coordination, and implementation. The LCE activity stages functionally interrelate in the hierarchical structure of business process. Horizontal PDCA occurred on each function and vertical PDCA occurred between the hierarchical functions facilitate LCE implementation. It is the first time to develop a business process model for pharmaceutical LCE. Interestingly, the structure of the model focused on pharmaceutical LCE is equivalent to the models which have been designed to describe plant operation safety management (Fuchino and Shimada, 2003; Fuchino *et al.*, 2007). This shows that structure of this study's template describing PDCA management is common between several industrial categories. Naka (2011) implied the commonality and this study explained it.

In this model, the product information, such as desired product performance and critical quality attributes, is stored in the Design product stage. Process information is clearly compartmentalized in the Design recipe, Design facility, and Produce stages. The activity model clarifies the boundary of business process and provides an overall information map from which traceable information can be extracted for specific objectives. The clear boundary avoids the multiplication and omission of business process. This framework is effective for constructing a system to organize complex information. The ontology-based knowledge integration framework has been studied and is used for modeling guideline knowledge and mathematical knowledge generated through the research and development process (Venkatasubramanian, 2006; Zhao, 2006). Purdue University introduced a method of

constructing the ontology for pharmaceuticals engineering and application (Hailemariam, 2010a; Hailemariam, 2010b). If ontology is designed without activity models, it may not be free from excess and deficiency. An activity model is necessary prior to designing ontology-based information infrastructures. The information management system built by Purdue University's method, whose boundary condition is clarified by the use of our activity models, could become a highly useful tool for pharmaceuticals development.

This section showed that LCE is accomplished not by the simple circular sequential configuration of the five engineering stages but by hierarchical horizontal and vertical PDCA across these stages. By designing business process management systems based on the activity model of this section, thorough and bias-free information handling can be realize. A management system built on the basis of the activity model is explained in the next section. This activity model-based approach supports extensive business process of projects, development phases, and business organizational structures, and thus facilitates a holistic and proactive LCE implementation for continuous quality improvement.

3.3 Activity Model-based Management

3.3.1 Introduction

Section 3.2 proposed a structure for a business process for LCE. The business process described in our activity model is not a one-way process. The model defined horizontal and vertical PDCA processes with the intent to implement repetitions in process improvement from early to late stages. As shown in Figure 3-5, management of personnel and technical factors is required to propel the business process defined on the model. The management function monitors the status of factors and analyzes the monitoring results by comparing them with the model. For personal factors, the management function analyzes whether employees appropriately understand the business process and cooperate in carrying out activities; management also decides to output directives and plans for training, and reorganizes personnel as needed. For technical factors, the management function analyzes whether technologies, procedures, infrastructures, and support tools for propelling activities work soundly; management also judges technical response if it is necessary to output directives and makes plans for updating and installing the factors. These personnel and technical factors are internal factors. In addition, the management function also monitors

external factors, such as changes in regulations, shifts in business structures, and technical innovations and outputs directives and plans to internal factors as required. There are various possible approaches to monitor the status of personal, technical, and external factors, but in this study, we do not focus on monitoring approaches in detail. Instead, we explain a framework for analyzing the monitored results and commencing actions to improve the current status. In this section, the continuous management of LCE is explained. Production process improvement is based on substantial systems for implementing change management. We propose systematized business processes for doing so.

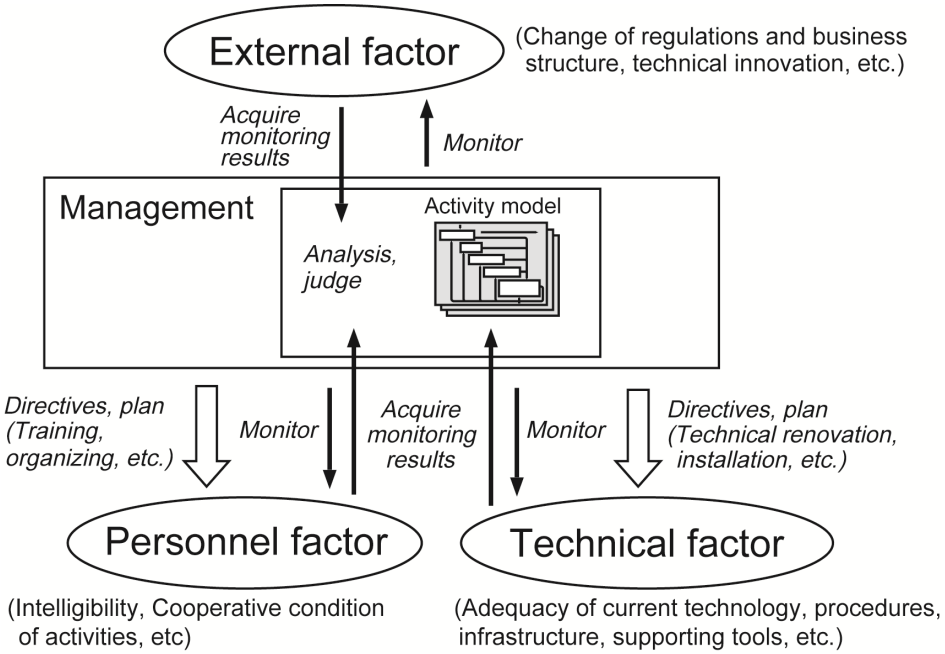


Figure 3-5 Management of business processes.

3.3.2 Preparation of LCE

In Section 2.2, some major outcomes are written in the overall outline of business process. In current industries, contents of the outcomes are decided by experts' experiences and the origin of them is unclear. In this section, we explain the business process to determine the contents of the outcomes on the model.

Quality target product profile is the basis of design for development of the pharmaceutical product including intended use in clinical setting, route of administration, dosage form, pharmacokinetic characteristics, and other drug product quality criteria (e.g., sterility, purity, and stability) appropriate for the intended marketed product (ICH, 2010). An example of a written sheet of the quality target product profile is Table 3-1. This information

is determined by business planning, drug discovery, and preclinical studies. A critical quality attribute is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate range or distribution to ensure the desired product quality. The determined example of critical quality attributes is Table 3-2. On the activity model, the quality target product profile sheet and the critical quality attributes list are handled in the activity A0: Execute process LCE for pharmaceuticals (Figure 3-6). This figure is abstract of Figure 3-3 focusing on handling of the quality target product profile and the critical quality attributes. The quality target product profile is served to activities A1 and A2 as control. In the activity A2, risk assessment for LCE implementation on the basis of the sheet is performed by using assessment procedures and available information and resources. The assessment results including critical quality attributes list and LCE implementation plan are served to activities A3-A7. Risk review is performed by activity A6 with risk assessment result from activity A2 and LCE implementation results from activity A3-A5. If activity A6 judges the selected critical quality attributes are insufficient, it is indicated that the assessment procedures served to activity A2 at the planning should be improved. In this case, the activity A1 asks for improvement of it to the activity A7. If given quality target product profile is difficult to realize in current performance of process engineering, change proposal to the plan is output to the upper layer. The quality target product profile sheet, risk assessment results, LCE implementation plan, implementation results, and risk review results are recorded in the activity A7. The information is used to improve risk assessment procedures and to serve as available information for the next LCE implementation case. The proposed business process enables to evolve PDCA cycle in critical quality attribute determination from quality target product profile.

Critical quality attributes determination follows process parameters risk assessment. Business process for this assessment is prepared in several activity layers. A set of parameters in a process, classification of them, contributing level to quality and performance, and risk mitigation plans as process characterization studies are summarized. Classification of process operation and behavior, which is explained in the following section 4.2, reflects parameter's importance, controllability, and relationship to the other processes. An example of process parameters risk assessment result in production cultivation step is shown in Table 3-3. Black boxes with white characters indicate the activities where information surrounded by bold lines is handled. The activities numbers correspond to Figure 3-2. First, a set of parameters of

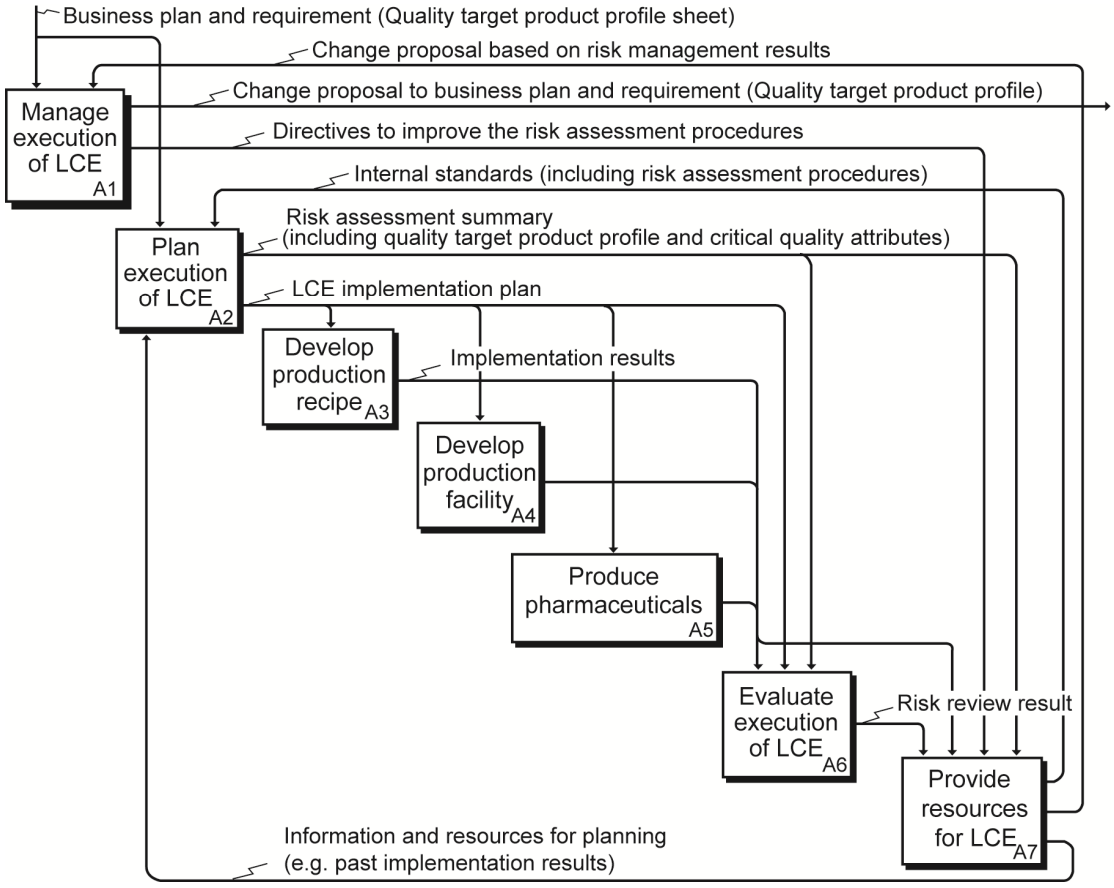


Figure 3-6 Handling of the quality target product profile sheet in A0 activity.

production culture step are determined in the activity A343: Develop recipe of upstream process. In the activity A343, activity A3432 (plan development of recipe of upstream process) outputs candidates to investigate a recipe as a development plan and activity A3435 (Develop recipe of production cultivation process) outputs the parameters list. The results are reviewed in activity A3437 (Evaluate development of recipe of upstream process) and served to activity A3438 (Provide resources for development of recipe of upstream process). In the activity A3438, results are written as shown in Table 3-3. Second, this result is also served to activities A36 and A37 via activity A341. Classification of the parameters is performed in the activity A3. Third, risk of the parameters on quality and process performance is assessed in activity A0. Forth, risk mitigation plan as process characterization studies are determined in activity A3. The all results are aggregated into activity A7. In the four activities, PDCA is carried out as explained above. Determining process parameters' risk by this business process with PDCA, listing of process parameter items, classification accuracy, relevance of risk decision, and risk mitigation planning strategy can be improved.

In the same way, the production control chart of production culture step (Table 3-4) is designed and the activities determining the contents of the charts are clarified. Although templates of production control charts are available in companies, business process to develop them is still unclear. Therefore, it spends long time to develop them by only personal contemplation and it is difficult to find wrong business functions from developed charts in case of deviations and changes. In the Table 3-4, the parameters to be controlled and their classification are determined in activity node of A343 and A3, respectively. Activity node means here that activity set in the node (e.g., activities of A1-A7 are in activity node A0). Quality-related and performance-related items are determined in activity node A0. Control limits are determined in activity node A3 with the rationale clarified by process characterization studies, past manufacturing results, process performance qualification results, and past typical ranges. The control limits are summarized in activity node A53. In order to achieve robust manufacturing, operation limit is set by facility or operation design determined in activity node A44. The results of manufacturing are obtained in the node A54. Analytical methods and status of them are summarized in activity node A36. The production control chart of cleaning verification of a tank is designed as in Figure 3-5. Measurement items and classification are determined in activity node A0. Control limits and setting rationale are determined in the node A53. Analytical procedures are determined in the node A36. The results of manufacturing are obtained in the node A54. Change management of this chart is a subject of the next section.

As explained above, explicitly defined business process enables to find which activities create a certain item in an outcome and which information is used to create it. The business process related to the item in the outcome contains plans, procedures, engineering standards, and etc. A set of business process to determine an outcome is defined as a protocol. The protocol is implicitly used during business processes are performed. The protocols are redesigned on the basis of the activity model. The items of outcomes can be designed without omission and procedures and reference information can be maintained. By using the redesigned protocol, the change management process could be revealed in case of any error in process LCE. Lean improvement occurs among diverse activities and the otherwise diverged information is merged.

Table 3-1 Quality target product profile sheet. This is handled in the activity node A0: Execute process LCE for pharmaceuticals.

Product Name		**Market aspects**		**Clinical aspects**						**Other comments**
Product name	**Product code**	**Market region**	**Commercial size**	**Indication**	**Target age**	**Molecular design**	**Action mechanism**	**Dose**	**Route of administration and dosage form**	
Product A	ABC-123	USA	10,000 /year	Indolent non-Hodgkin's Lymphoma	adult only	humanized IgG1	Binding to a tumor cell surface antigen, Lymph-A, and stimulating B cell killing by majorly ADCC activity	10 mg/kg for 6weeks (on determination)	Intravenous Ampoule added in intravenous drip	Aggregates induce adverse effect as agonistic action.
Product B	ABC-456	EU, USA	100,000 /year	Bronchial Asthma	adult and child (in future)	glycoprotein	Antagonistic action on leukotriene receptor, LR-1	15 mg/kg for 2weeks (on determination)	Hypodermic Hypodermic syringe	Light sensitive

Table 3-2 Critical quality attributes assessment list. This is handled in the A0: Execute process LCE for pharmaceuticals. Factor-1, 2, and 3 are risk evaluation items such as efficacy, safety, pharmacokinetics, uncertainty, and likelihood. RA: risk assessment.

Product A						
Product quality attribute			**RA procedure #1**		**RA procedure #2**	**Risk score**
			Factor-1	**Factor-2**	**Factor-3**	
product-related	Aggregates		12	12	10	12
	Fragments		10	10	10	10
	Glyco-variants	Non-glycosylation	10	6	6	10
		Non-consensus glycosylation	10	2	10	10
		Galactose contents	10	2	2	10
		Fucosylation	10	2	6	10
		Sialylation	10	6	2	10
		High Mannose	10	6	6	10
	Oxidants		10	6	10	10
	Deamidated isoforms		10	6	2	10
	C-terminal truncation variants	Lys heterogeneity	2	2	2	2
		Amidation	2	2	6	6
	N-terminal isforms		2	2	6	6
	Cystein-linked variants	Free thiol	6	6	6	6
		Trisulfide	2	6	2	6
		Cystenylation	2	6	6	6
	Isomerized isforms		2	6	6	6
	Glycated variants		2	2	2	2
process-related	HCP		-	12	-	-
	DNA			12		
	ProteinA			12		
	Raw material derived contaminants			12		

Table 3-3 Process parameters risk assessment result. C: Critical, K: Key, Blank: non-key. Abbreviations in classification column are explained in Table 4-1. Black boxes with white characters indicate the activity nodes where information surrounded by bold lines is handled. The activities numbers correspond to Figure 3-2.

Process parameter in production cultivation step		*A0* Critical quality attribute (In-process quality attribute)					Process performance attribute			*A3*
A343 Item	*A3* Classification	Aggregates	Fragments	Glyco-variants	Oxidants	Deaminated isoforms	Yield	Cell viability	Total population doubling level	Risk mitigation plan
Media pH	Adj-IA						K	K	K	PC study #1
Media osmolality	Adj-IA						K	K	K	PC study #1
N-1 cell density	Adj-IA								K	PC study #2
N-1 cell viability	Adj-IA								K	PC study #2
N-1 pH	Adj-IA								K	PC study #2
Media conditioning temperature	CS								K	PC study #3
Media conditioning agitation	MA									NA
Inoculum cell density	CS						K	K	K	PC study #4
Inoculum cell viability	CS						K	K	K	PC study #4
Osmolality	MS			K		K	K	K	K	PC study #5
Temperature	CS			C	K	K	C	K	K	PC study #6
pH	CS	K	K				K	K	K	PC study #6
Dissolved oxygen concentration	CS							C		PC study #7
Dissolved CO_2 concentration	MS	K	K	C			K	K	K	PC study #7
Antifoam addition volume	CS									NA
Agitation rate	MA									NA
Tank pressure	CS									NA
Glucose concentration	MS						C		C	PC study #8
Lactate concentration	MS									NA
Feed volume	MA						C		C	PC study #8

Table 3-4 Production control chart of production culture step. Abbreviations in classification column are explained in Table 4-1. PC: process characterization study, PPQ: process performance qualification. Analytical procedures are omitted. Black boxes with white characters indicate the activity nodes where information surrounded by bold lines is handled. The activities numbers correspond to Figure 3-2.

Process parameter in production culture step		Controls				Limit setting rationale	Operability	Results			
Item	Classifi-cation	Set point	Control range	Action limit	Alert Limit			3σ	Lot 1	Lot 2	Lot 3
A343 ia conditioning temperature	CS	37°C	±1	-	-	PC study #3	Set point±0.3	...	...	...	...
Inoculum cell density	CS	0.4 million/mL	±0.1	-	-	PC study #4	Set point±0.05	...	...	...	...
Inoculum cell viability	CS	-	90%≤	-	-	PC study #4	Uncontrollable	...	...	...	...
Osmolality	MS	-	-	-	≤400 Osm	PC study #5	Uncontrollable	...	...	...	...
Temperature	CS	37°C	±1	-	-	PC study #6	Set point±0.3	...	...	...	...
pH	CS	7.0	±0.2	-	-	PC study #6	Set point±0.1	...	...	...	...
Dissolved oxygen concentration	CS	50%	±15	-	-	PC study #7	Set point±20	...	...	...	...
Dissolved CO_2 concentration	MS	-	-	≤20%	≤15%	PC study #7	Set point±3	...	...	...	...
Antifoam addition volume	CS	-	≤3 L	-	-	Typical range	On demand	...	...	...	...
Agitation rate	MA	15 rpm	±3	-	-	Typical range	Set point±0.5	...	...	...	...
Tank pressure	CS	20 kPa	±3	-	-	Typical range	Set point±1	...	...	...	...
Glucose concentration	MS	-	-	0.5 g/L≤	1.0 g/L≤	PC study #8	Target±0.3	...	...	...	...
Lactate concentration	MS	-	-	-	Within 3σ	3σ of past results	Uncontrollable	...	...	...	...
Feed volume	A3	1000 L	±100	-	-	PC study #8	±2 L/shot	...	...	...	...
A0 Aggregates	IA	-	-	≤3%	Within 3σ	PPQ and PC study #6, 7	-	...	...	...	...
Fragments	IA	-	-	≤0.8%	Within 3σ	PPQ and PC study #6, 7	-	...	...	...	...
Glyco-variants	IA, PPA	-	-	0.5-1.5%	Within 3σ	PPQ and PC study #6, 7	-	...	...	...	...
Deamidated isoforms	IA, PPA	-	-	≤2%	Within 3σ	PPQ and PC study #6	-	...	...	...	...
Host cell protein	IA	-	-	-	≤200000	PPQ and PC study #4, 6	-	...	...	...	...
Yield	PPA	-	-	4.0-6.0 kg	Within 3σ	PPQ and PC study #3-8	-	...	...	...	...
Cell viability	IA, PPA	-	-	70%≤	Within 3σ	PPQ and PC study #4, 6	-	...	...	...	...
Total population doubling level	PPA	A53 -	-	≤30	≤25	A3 and PC study #4	A43 -	A54 ..	...	...	...

Table 3-4 (continued)

Process parameter in production culture step		Analytical procedures				
Item	Classification	SOP #	Analyzer	Accuracy	Sampling	Status
Media conditioning temperature	CS	SOP-010	TE-101	±0.1	Inline	Validated
Inoculum cell density	CS	SOP-011	Cell counter	±10000	100 mL (n=1)	Qualified
Inoculum cell viability	CS	SOP-011	Cell counter	±0.1		Qualified
Osmolality	MS	SOP-012	Osmolality meter	±1		Qualified
Temperature	CS	SOP-013	TE-201	±0.1	Inline	Validated
pH	CS	SOP-014	pH meter	±0.1	30 mL (n=1)	Qualified
Dissolved oxygen concentration	CS	SOP-015	PH-201	±5	Inline	Validated
Dissolved CO_2 concentration	MS	SOP-015	CD-201	±0.1	Inline	Validated
Antifoam addition volume	CS	BPR	Scale-123	±5	NA	NA
Agitation rate	MA	SOP-016	AG-201	±0.5	Inline	Validated
Tank pressure	CS	SOP-016	PE-201	±1	Inline	Validated
Glucose concentration	MS	SOP-017	Bioanalyzer	±0.1	30 mL (n=1)	Qualified
Lactate concentration	MS	SOP-017	Bioanalyzer	±0.1	30 mL (n=1)	Qualified
Feed volume	MA	BPR	Flow meter	±2	NA	Validated
Aggregates	IA	SOP-111	Size exclusion chromatography	TBD	5 mL (n=3)	Under development
Fragments	IA	SOP-111	Size exclusion chromatography	TBD	5 mL (n=3)	Under development
Glyco-variants	IA, PPA	SOP-112	Isoelectric focusing electrophoresis	NA	200 mL (n=1)	Qualified
Deamidated isoforms	IA, PPA	SOP-113	Ion exchange chromatography	±0.02	10 mL (n=1)	Qualified
Host cell protein	IA	SOP-114	ELISA	TBD	10 mL (n=3)	Under development
Yield	PPA	BPR	Calculation from protein conc.	NA	NA	NA
Cell viability	IA, PPA	SOP-011	Cell counter	±0.1	100 mL (n=1)	Qualified
Total population doubling level	PPA	BPR	Calculation from cell density	NA	NA	NA

A36

* Item and classification are copied from previous table for understandability.

Table 3-5 Production control chart of cleaning verification of a tank. Abbreviations in classification column are explained in Table 4-1. Black boxes with white characters indicate the activity nodes where information surrounded by bold lines is handled. The activities numbers correspond to Figure 3-2. TOC: total organic carbon concentration, LAL: *Limulus Amebocyte* lysate assay, ELISA: enzyme-linked immunosorbent assay.

Process parameter in cleaning verification of tank-A		Controls				Limit setting rationale	Operability	Results			
Item	Classification	Set point	Control range	Action limit	Alert Limit			3σ	Lot 1	Lot 2	Lot 3
Appearance	IA	-	-	No rouge	-	Standard limit	-	...	...	...	...
Rince pH	IA	-	-	6.0-7.0	6.5-7.0	Standard limit	-	...	...	...	...
Rince conductivity	IA	-	-	<5 μS/cm	<2 μS/cm	Standard limit	-	...	...	...	...
Rince TOC	IA	-	-	<1 ppm	<0.5 ppm	Report #123	-	...	...	...	...
Rince ELISA	IA	-	-	<10 ppb	<5 ppb	Report #456	-	...	...	...	...
Rince bioburden	IA	-	-	<10cfu/10mL	<3cfu/10mL	Standard limit	-	...	...	...	...
Rince endotoxin	IA	-	-	<0.4 U/mL	<0.2 U/mL	Standard limit	-	...	...	...	...
Swab TOC	IA	-	-	-	Within 3σ	Monitoring only	-	...	...	...	...
Swab bioburden	IA	-	-	-	Within 3σ	Monitoring only	-	...	...	...	...
Swab endotoxin	IA	-	-	-	Within 3σ	Monitoring only	-	...	...	...	...

A0 ***A53*** ***A54***

Analytical procedures				
SOP #	Analyzer	Accuracy	Sampling	Status
SOP-311	NA	NA	NA	Qualified
SOP-312	pH analyzer	±0.1	10 mL (n=1)	Qualified
SOP-312	Conductivity meter	±0.05	10 mL (n=1)	Qualified
SOP-313	Offline TOC analyzer	±0.1	100 mL (n=5)	Qualified
SOP-314	ELISA	±1	5 mL (n=3)	Under development
SOP-315	Colony assay	NA	200 mL (n=1)	Qualified
SOP-315	LAL	±0.02	10 mL (n=1)	Qualified
SOP-313	Offline TOC analyzer	±0.1	n=3	Qualified
SOP-315	Colony assay	NA	n=1	Qualified
SOP-315	LAL	±0.02	n=1	Qualified

A36

3.3.3 Implementation of LCE

Process development and production are implemented by protocols designed on the model. The implementation results are evaluated and recorded in the outcomes. The recorded results are stored in Provide resources activities. For example, manufacturing results are recorded in the production control chart in Table 3-4. The format of outcomes and procedures correspond to technical factors in Figure 3-5. If the implemented results are evaluated to find some problems, directives and plans to redesign protocols are output by Manage activities.

The maintenance of protocols is triggered if a manufacturing result deviates from the control limit. For example, if the aggregate in a manufacturing lot is 4%, process performance qualification and process characterization study number 6 and 7 are investigated. Controlled parameters operability and results related to the process characterization study number 6 and 7, which are temperature, pH, dissolved oxygen concentration, and dissolved CO_2 concentration, are also investigated. If the osmolality is identified to affect the aggregates, the engineering standard of process characterization planning in the activity A3 will be changed and process characterization study number 5 will add the investigation into effect on aggregates. If other new items are identified, a parameters listing standard in activity A343 will be changed. Actually, the change management includes complex business process. If technical factors in Figure 3-5 such as the templates of outcomes, procedures, and tools are changed without thoughtful consideration, other unexpected problems can occur. The detailed change management based on the activity model is explained in Section 3.3.4.

3.3.4 Change Management

In change management, both quality and quantity of information transaction are important. Overview of the hazard identification and risk assessment process for change management is explained in Occupational Health and Safety Assessment Series (OHSAS) 18002; 2008 (OHSAS, 2008). In this standard, change management is performed by cycle of hazard identification, risk evaluation, determination of countermeasures, and implementation of the countermeasures. Although this scheme shows necessary steps for change management, PDCA function occurring in each step is unclear. We divide change management process into four steps of notification of problem, investigation and suggestion for improvement, risk assessment for a change plan, and implementation (Figure 3-7). These steps cover the risk

management process explained in ICH Q9 (ICH, 2005) as well as OHSAS's scheme. The change steps are developed on the activity model and manage, control, and implement functions are defined to perform PDCA cycle in each step. Manage function judges adequacy of current change management system and encourages continuous improvement. Control function makes the implementation plan, controls progress of an improvement process, checks some problems, and reports the results. Change activities are implemented under the control and manage functions. During a case is processed through the four steps, PDCA of the improvement management system is carried out by manage, control, and implement functions. This structure can be expressed on the activity model because our model is designed to achieve hierarchical horizontal and vertical PDCA. Past information is aggregated in Provide resources activities and served for current implementation. Therefore, the reference information served from the Provide resources is upgraded continuously. Continuous improvement is accomplished by this horizontal and vertical information exchange and upgrade of Provide resources in all layers.

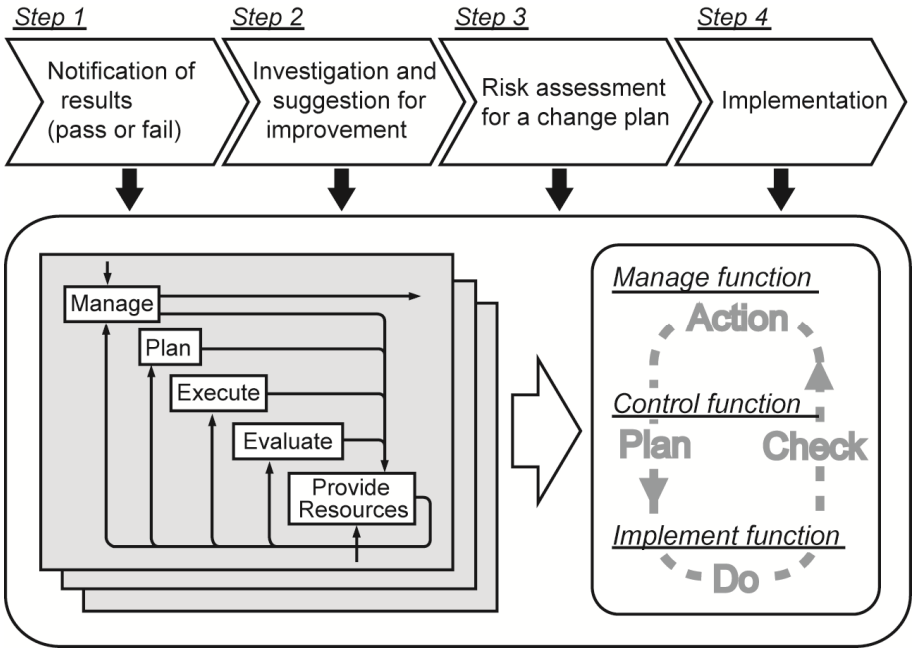


Figure 3-7 Scheme of change management process.

The activity model-based change management approach is explained by using a case study that analytical instruments and procedures are changed to improve efficiency of cleaning verification operation between batches and increase the number of batches per a year. Overall picture of the activity model is shown in Figure 3-8. Limited business process is

shown for simplification. Bold broken lines separate design recipe, design facility, operation, and maintenance stages. A problem notification as the trigger of change management is output from the meshed activity A553: Execute regular maintenance. It is shown that information for the change management is expanded to overall stages via design product stage. Detailed flows in each step are explained below.

3.3.4.1 Step 1: Notification of Problem

In the situation that no problem occurs, results are confirmed and change process is not started. When a result is judged to be a problem, change process is started by the trigger notification of the problem. The trigger contains operational malfunction, improvement suggestion, and change of the external situation. Operational malfunction means process deviation, defect or abnormal sign of equipment, procedural error, and unsatisfied result, for example, deviation of pH from a control limit. Improvement suggestion is construed as malfunction from an ideal situation, for example, advanced control of pH is achievable by installation of new device. Change of the external situation forces operational changes, for example, installation of new device is required to conform to a new regulation.

In the case study, the trigger notification is output from activity A553 as cleaning verification procedure is complex and time-consuming (Figure 3-9). The trigger notification is served to activity A555: Evaluate maintenance. The A555 evaluates the potential risk in the notified information as far as considerable in this layer and outputs it to activity A556 as evaluation report. Provide resources integrates the evaluated report and related information which has been stored and outputs risk information to the Manage activity. In the case study, the activity A556 outputs that inefficient procedure for cleaning verification takes place in all batches and extends total maintenance time. The A555 evaluates necessity to notify to upper layer and activity A551 judges it. If Manage activity decides to notify the risk information to the upper layer, it is output to the upper layer's Evaluate activity as notification of problem. Business process in the upper layer is same as above. Activity A57 outputs risk information that inefficient procedure for cleaning verification decreases the number of production cycles, hence increases cost per batch. Upper layer integrates information provided by the lower layers and aggregates it into more essential risk information.

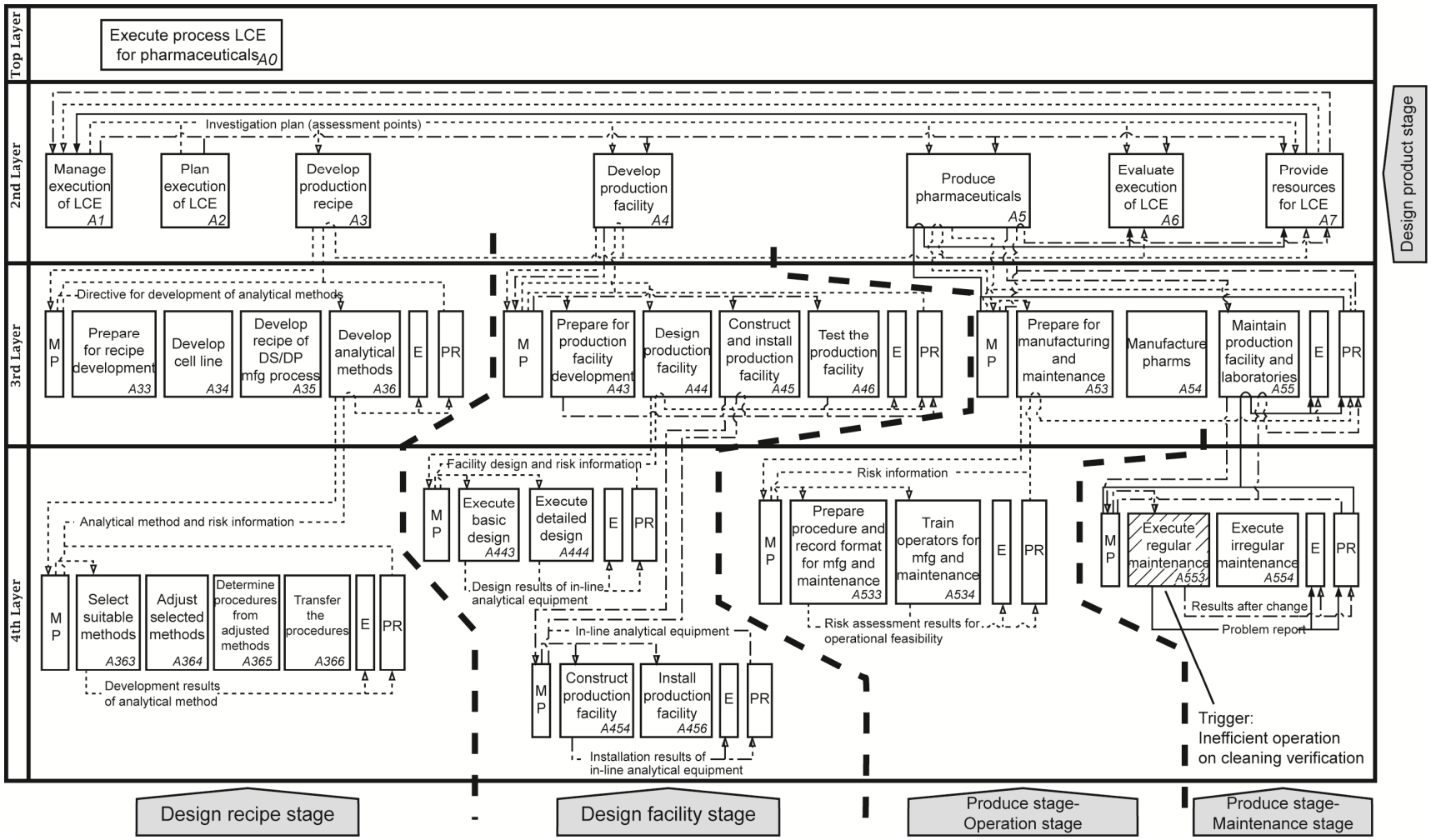


Figure 3-8 Overall picture of the activity model. Bold broken lines show boundaries to separate design recipe, design facility, operation, and maintenance stages. Solid, dashed, and dash-dotted lines represent information of step 1: notification of problem, step 2/3: causal investigation and risk assessment, and step 4: implementation, respectively. M: Manage, P: Plan, E: Evaluation, PR: Provide resources, Pharms: Pharmaceuticals, DS/DP: Drug substance and drug product, and mfg: Manufacturing.

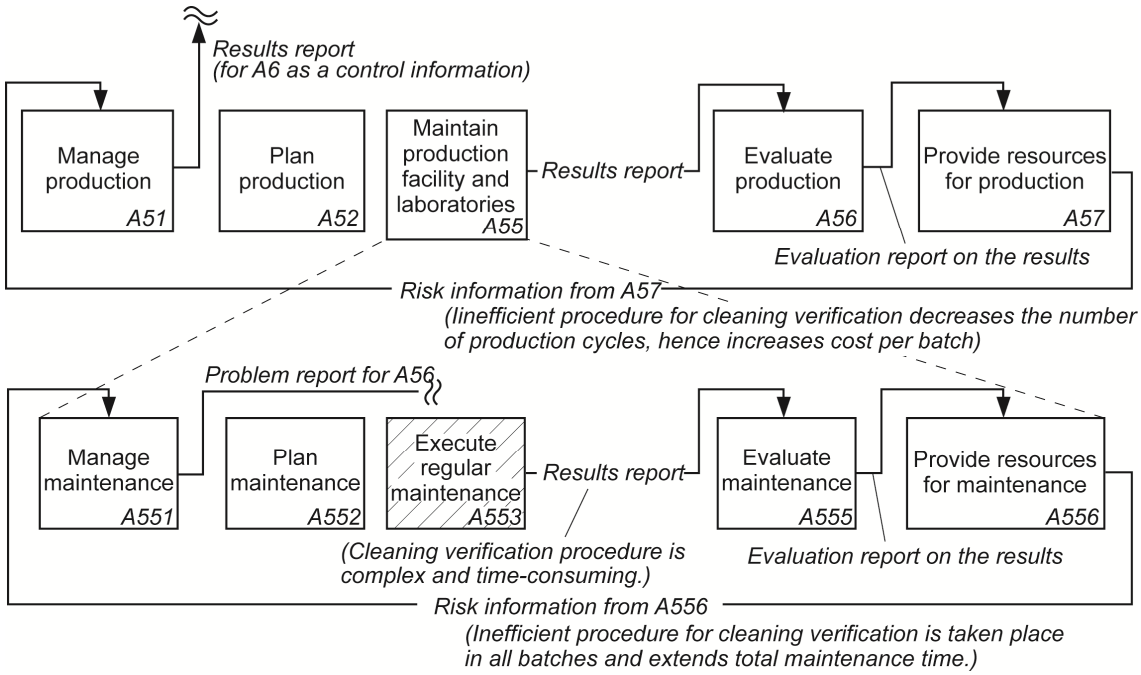


Figure 3-9 Activity model on step 1: notification of problem.

3.3.4.2 Step 2: Investigation and Suggestion for Improvement

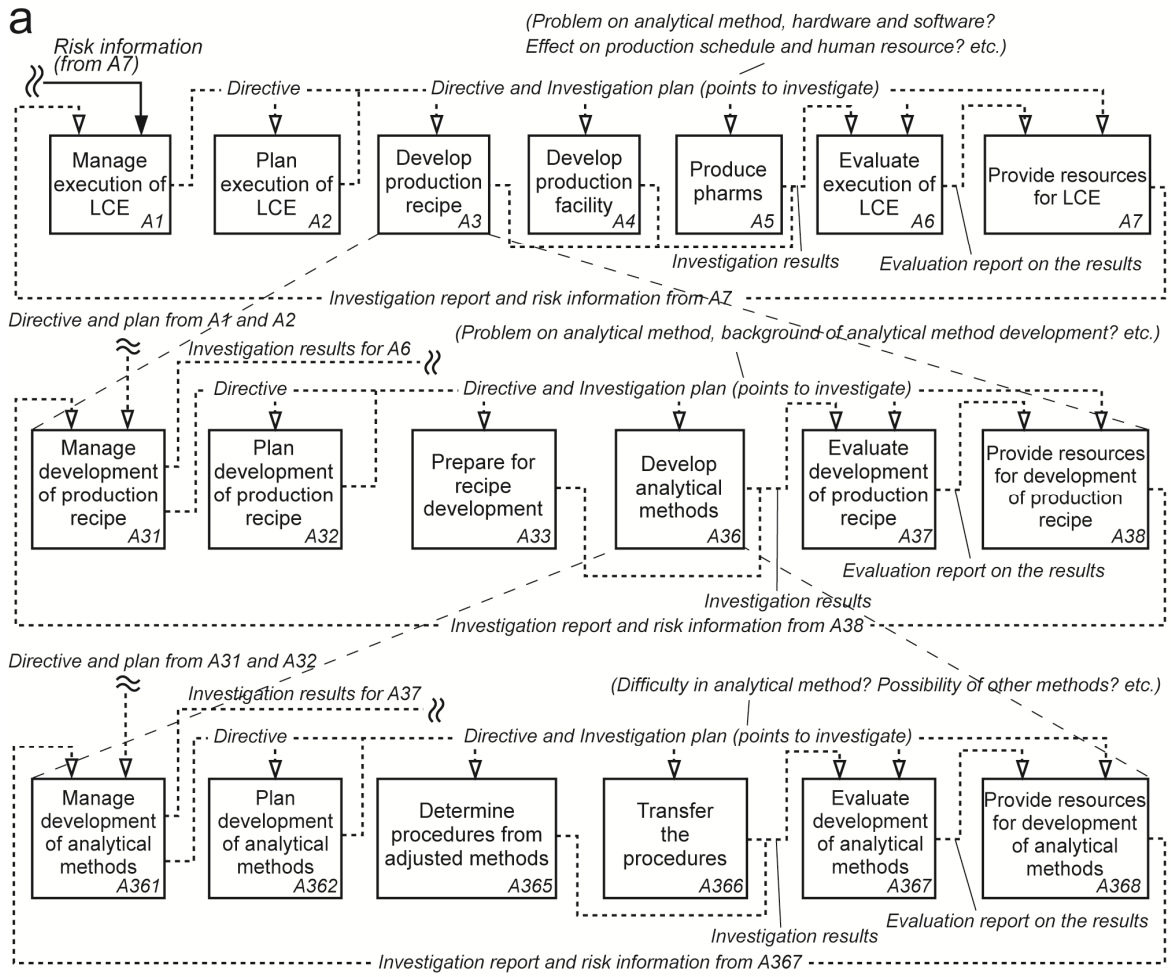
The Manage activity, which judges not to notify to upper layer, outputs directives to investigate causes and effects. It asks suggestion to improve (Figure 3-10). In case of change of the external situation, the step 1 is skipped and change management process is started from the step 2. The Plan activity outputs the investigation plan containing investigation objects. An engineering standard is served from Provide resources for this planning. In the case study, activity A2 plans to investigate analytical procedure, sampling procedure, skill level of workers, and influence on production cycle time. This planning is guided by a prepared form explained in Section 3.3.5. Based on this plan, activity A31 outputs concrete directives to the activities in A31's layer and then activity A32 plans to investigate detailed analytical procedures. In the lower layer, subsequently, activity A362 plans to investigate required time for an impurity analysis, the number of the samples, and the complexity of the analytical procedures. In this way, the plans are developed in more practical in the lower layers.

According to the plans, investigation is carried out and improvable items are suggested. Investigation results and improvement suggestions are evaluated and priority of the items is determined in the Evaluate activity. In the case study, activities A365 and A366 output that measurement procedure is proper, but measurement takes a long time due to old analyzers. Provide resources outputs risk information based on the investigation results, improvement suggestions, and stored information. Activity A368 outputs that inefficiency of

operation is caused by conventional analytical method and old instruments, so that introduction of the latest in-line analyzer may improve it. Information of the lower layers is gathered in the higher layer, and the root causes are identified. Then, appropriate improvement plans are prepared with priority evaluation (Figure 3-10b). All of the detailed assessment information is summarized in an expression which is familiar with the Manage activity so that the Manage activity can shorten the time for judgment. The Manage activity can acquire detailed information by tracing reports in the lower layers as needed.

3.3.4.3 Step 3: Risk Assessment for a Change Plan

Based on the suggestion gathered in the step 2, the Manage activity proposes a set of change items. In the step 3, risks to apply the change are assessed. As for risk assessment methods, refer publications (ICH, 2005; Vesper, 2006). In the case study, the activity A1 proposes introduction of the in-line analyzer, upgrade of old analytical instruments, and revision of policy and standard of cleaning verification (Figure 3-11a). The Plan activity outputs risk assessment points. For example, restriction of time and cost for the A43 and introduction feasibility from the point of view of equipment specification for the A44 are provided as assessment points. Risk assessment results based on the plans are served to the evaluate activity. The results contain feasibility of the change application, cost, schedule, and possible problems that occur after the change implementation. The Evaluate activity evaluates validity of the assessment results and summarizes the best course of actions. The Provide resources outputs summarized information for decision making of the Manage activity by considering the provided results and stored information. For example, the activity A446 outputs that minor modification of pipes is required, but cost and risk for introduction are small. Additional proposal to introduce it for other facilities is also output. Such an information development is also one of the functions of Provide resources. Since all facilities' designs are stored in the activity A446, it is possible to trigger the development beyond the walls of facilities. In the upper layer, risk in the change plan is clarified by integrating comprehensive information (Figure 3-11b). Consequently, the activity A7 reports to the activity A1 that introduction of an inline analyzer and new analytical instrument has a small risk, minor modification of pipes is necessary, about three months are totally required to prepare detailed procedural documents, and these changes should be applied to other facilities.



b

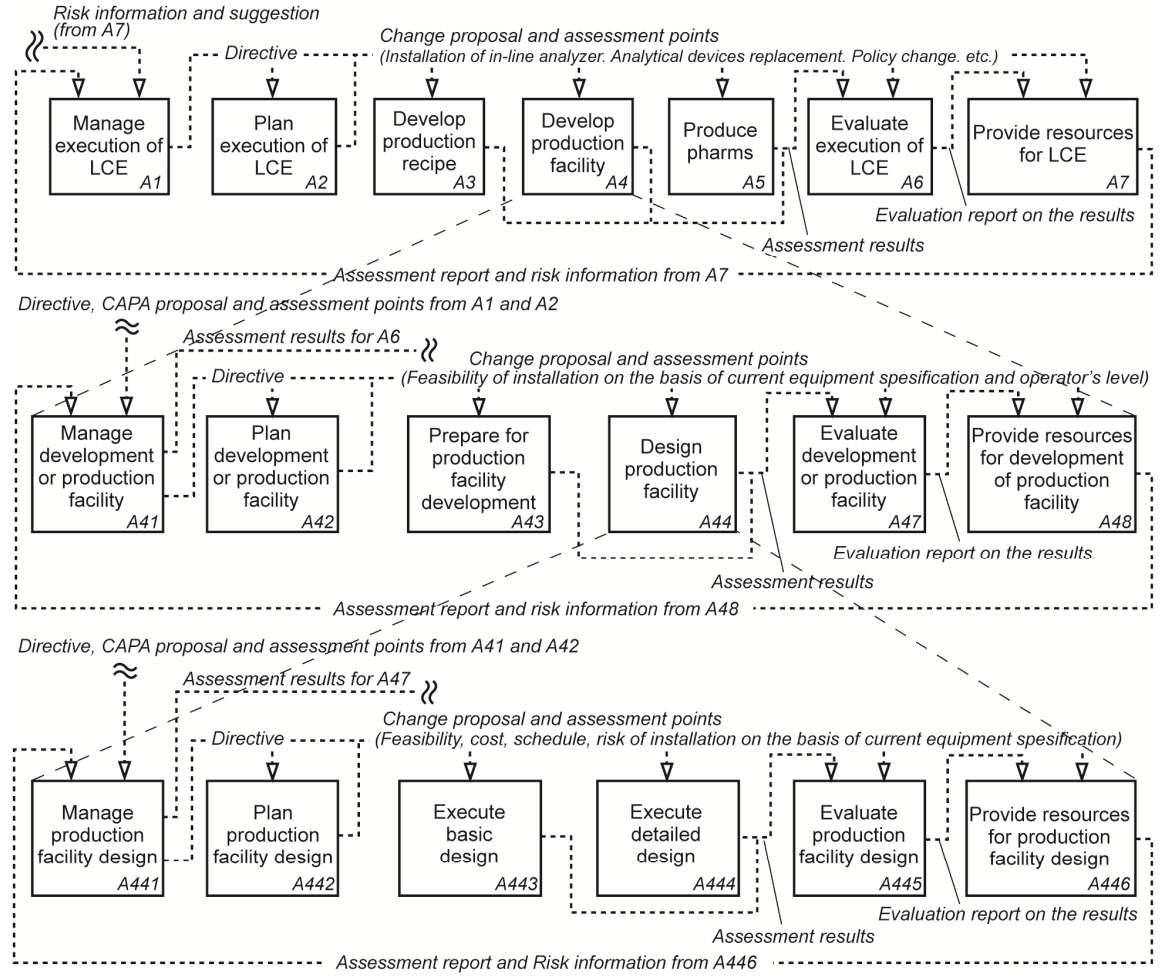
A7: Cost per batch can be decreased by solving inefficiency of cleaning verification. The efficiency can be improved by updating 1) policy, 2) analytical methods, and 3) analytical devices of cleaning verification.

aggregation

- A38: Inefficiency of operation is caused by conventional analytical method and old instruments. Policy for cleaning verification also should be changed to install new instrument such as in-line analyzer.
  - A337: Policy for cleaning verification is too complex to change.
  - A368: Inefficiency of operation is caused by conventional analytical method and old instruments. In-line analysis may be applicable.
    - A3656: The procedure of measurement cleaning verification samples is appropriate.
    - A3667: Transferred instruments for measurement of cleaning verification samples are outdated and analysis is too slow.
- A48: Facility design has no problem regarding inefficiency of cleaning verification.
- A57: Training procedure has no problem, but SOP for cleaning verification is too complex to familiarize operators. Policy for cleaning verification should be changed to simplify cleaning verification procedure. The complexity increases cost per batch.

Figure 3-10 Activity model on step 2: investigation and suggestion for improvement. a: activity model, b: brief description of investigation report and risk information output from each Provide resources activity. Codes started from A are ID number of each Provide resources. Abbreviation is same as caption for Figure 3-8.

a



b

A7: Risk is small to install in-line devices and new analyzers in the facility and the QC laboratory, respectively. Minor modification of piping is required. Installation to all facilities should be considered. Three months are required to prepare analytical procedure and documents. Regulatory risk should be carefully considered for in-line measurment.

A38: It requires a month to develop new analytical procedures. Survey of regulation about installation of in-line measurement is necessary.

A48: Risk of installation of in-line analyzer in the facility is small. Minor modification of piping is required.

A436: Document preparation for installation of in-line analyzer is easy.

A446: Minor modification of piping is required, but its risk is small. Installation in other facilities is recommended.

A4438: Risk on cost and schedule is small. Installation of in-line analyzer is applicable to other facilities.

A4447: Piping modification is required. Risk is small.

aggregation

A57: SOP preparation and operator training for new instruments is easy. It requires about two months to prepare GMP documents.

Figure 3-11 Activity model on step 3: risk assessment for a change plan. a: activity model, b: brief description of assessment report and risk information output from each Provide resources activity.

3.3.4.4 Step 4: Implementation

Based on gathered risk assessment results, the Manage activity decides the change items and change implementation is started (Figure 3-12). The Plan activity outputs the schedule, budget, specifications, and responsibility system. Because the risk has been already considered adequately, this implementation should progress smoothly. The implementation results are gathered from each layer to the upper layer and a change process is completed by accepting the results. If a new problem occurs at this step, a new change process is started for this problem.

As described above, this activity model-based system enables to record step-by-step information for decision making. Without this system, quality of decision could be different, dependent on intelligibility of personnel. Such a variation in quality can be minimized by modeling the experts' information structure. It is important for continuous improvement of change process to record not only what has been changed but also how and why the decision has been made for the changes to occur.

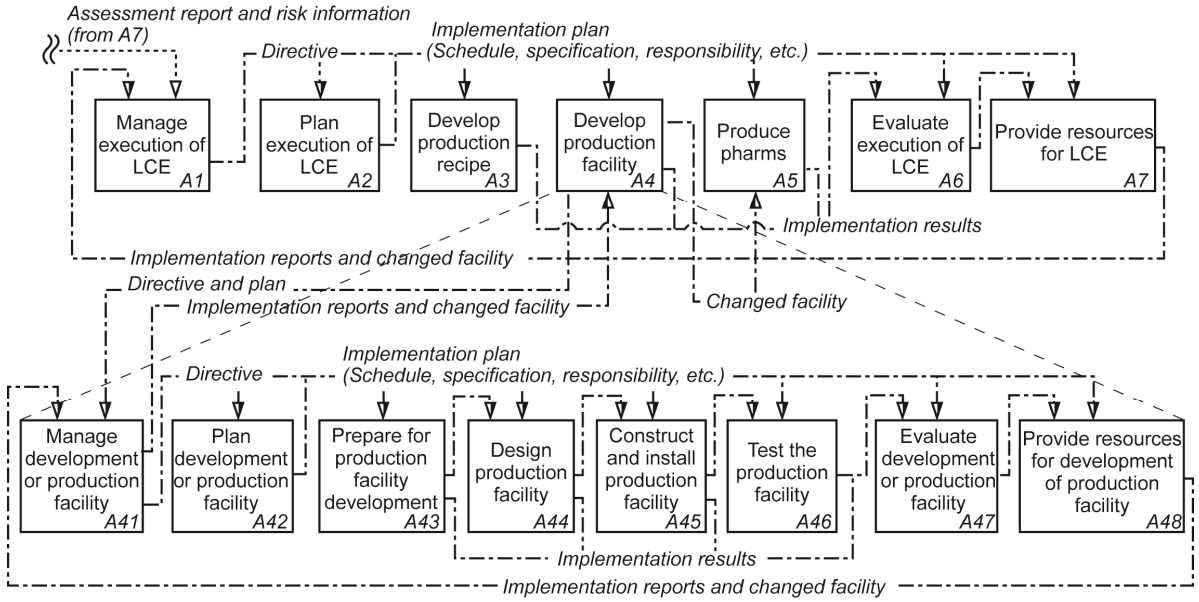


Figure 3-12 Activity model on step 4: implementation.

3.3.5 Continuous Improvement

The business processes in each step of a change management process are explained above. In this section, we introduce examples of engineering standards (and/or business rules) to support decision making. Continuous improvement of a change management system is achieved by reviewing engineering standards.

In Step 1: Notification of problem, guide forms such as Figure 3-13 are prepared to serve as engineering standards. In Figure 3-9, a trigger notification is produced from activity A553, evaluated in activity A555, and summarized in activity A556 as risk information. The summarized information is judged to notify the the upper layer in activity A551. These actions can be guided by such forms as those in Figure 3-13. Guide forms are prepared for each activity and objective. The contents of these guide forms are determined on the basis of the activity model. An example of the guide form for the problem notification in the activity A553 is shown in Figure 3-13a. It contains boxes for selecting the type of problem. These items are picked up by using past results recorded in activity A556 in which the results from activity A553 are gathered. The items for notification in the guide forms differ for different activities because the categories of possible problems differ from each other.

The guide form for the Evaluate activity A555 is shown in Figure 3-13b. The evaluation items refer to a PQCDSM framework (Ketsarapong *et al.*, 2012). PQCDSM is the abbreviation for is productivity, quality, cost, delivery, safety, and motivation (morale), respectively. To prepare an appropriate guide form, various existing tools and frameworks can be employed. In this study, we do not discuss which tool or framework is most appropriate for making each decision. To achieve a series of substantial business processes, the activity model-based approach integrates various management tools and frameworks employed in each activity. Activity A556 summarizes risk information, as in Figure 3-13c. Activity A551 judges the necessity to notify the upper layer by using the guide form in Figure 3-13d. This form for activity A551 reflects the structure of activity model. Activity A551 judges the necessity to notify from the point of view of cooperation of activities written in the model.

Guide forms for Step 2: Investigation and suggestion for improvement are shown in Figure 3-14. These examples are used to make an investigation plan for activities A2 and A32. Activities A2 and A32 can make the plans from the viewpoints of lower activities, because overall activities are explicitly and concretely defined in the model. The scope of the guide forms can be clarified based on the activity model. For the purpose of making a sound judgment to notify a case to the upper layer, items in the guide form are prepared considering the whole business process, as shown in Figure 3-13d. On the other hand, when an activity makes directives or plans for the lower layers, items in the guide form are prepared that include viewpoints of the current and lower layers.

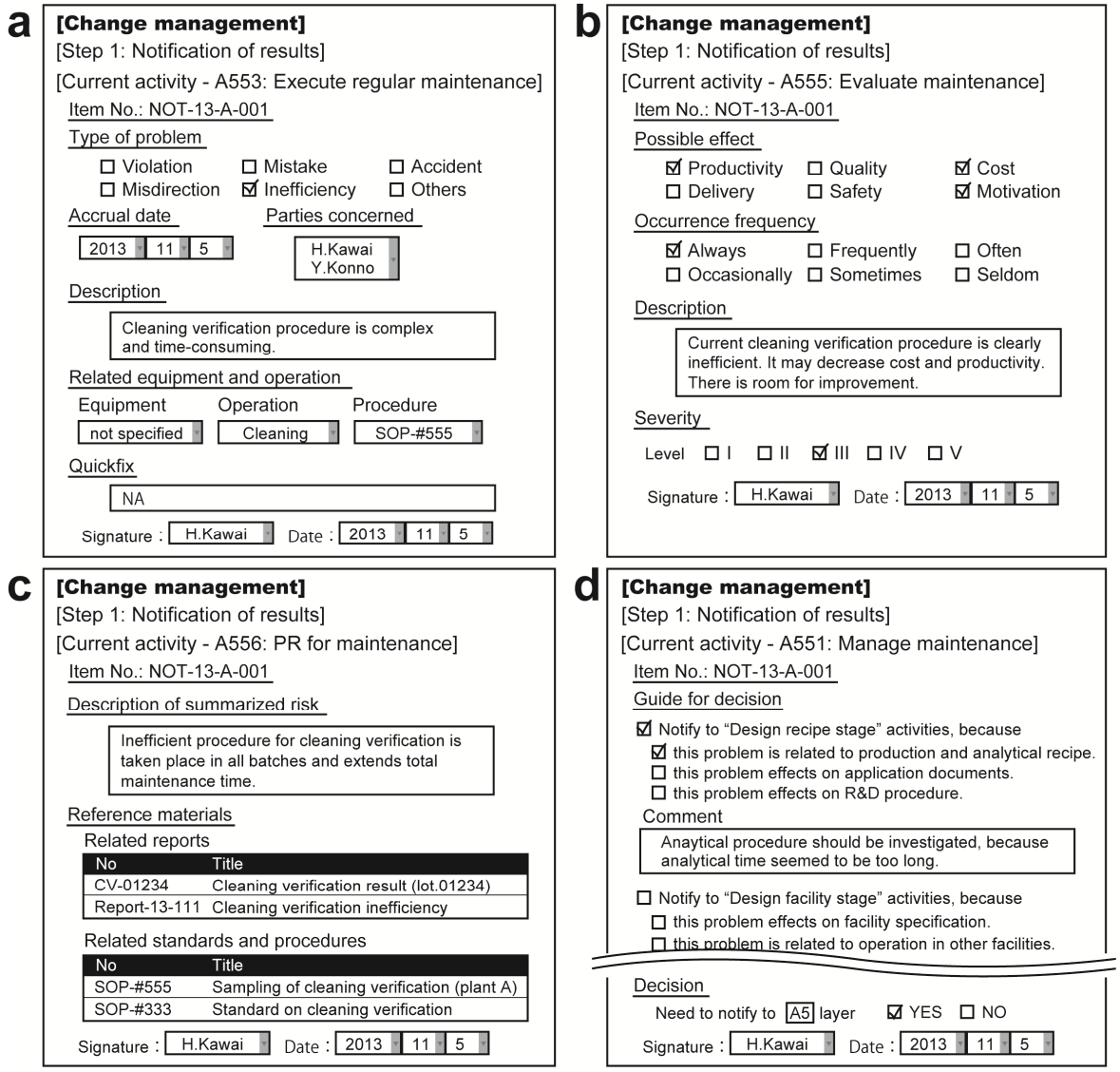


Figure 3-13 Examples of guide forms for notification of a problem in A55. Figure a, b, c, and d are for activities A553, A555, A556, and A551, respectively.

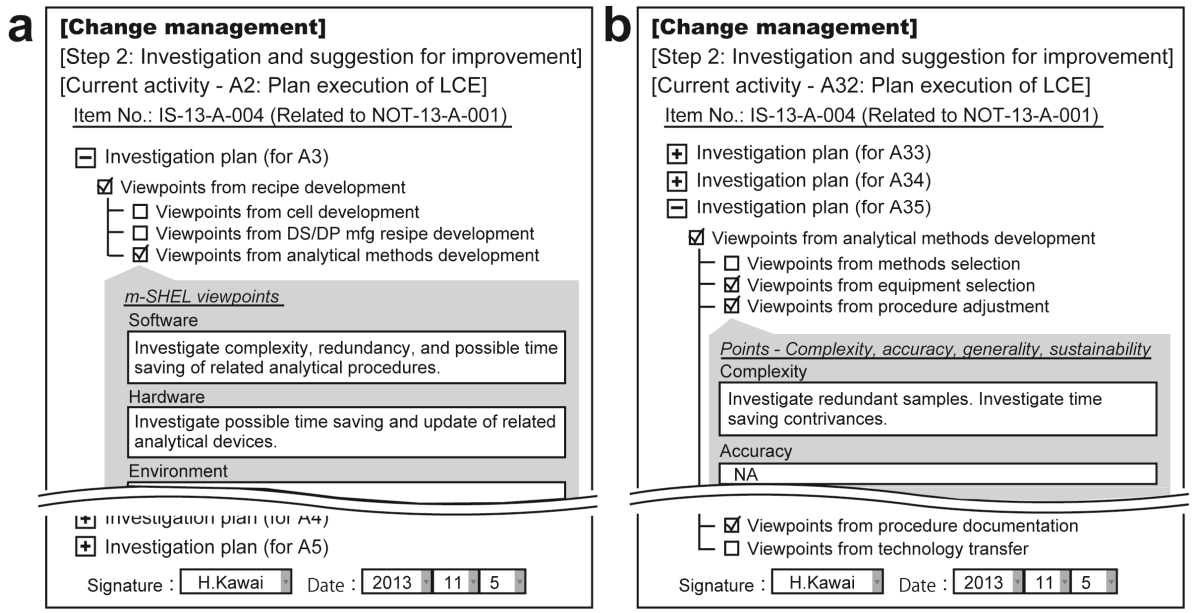


Figure 3-14 Examples of guide forms for investigation and suggestion for improvement for A2 (a) and A32 (b).

The m-SHEL model (Itoh *et al.*, 2004) is applied for detailed investigation viewpoints as shown in Figure 3-14a. The m-SHEL model classifies human factors into Software-Hardware-Environment-Liveware (SHEL) with their management (m). For error classification of human factors, the human behavioral model in the CCPS concept book (CCPS, 2007) and the error category in Lee's hazard identification (Mannan, 2005) can be applied. The concept of 4M-4E (Man, Machine, Media, Management, Education, Engineering, Enforcement, and Example) may be applicable for causal investigations (Mori *et al*., 2008). In Figure 3-14b, investigation points from viewpoints of procedure adjustment are divided into complexity, accuracy, generality, and sustainability. No references are used here to set these items. Although it is uncertain at the beginning what kind of concept is best for supporting each decision making, the guide forms can be continuously revised to be a satisfactory supportive tool.

In the case of a new experience without precedents, the decision has to be made by rule of thumb because the prepared guide form cannot be applied. However, since the guide form is revised through new experience, thereafter, intuition-dependent decision making is formalized. Therefore, the change management system improves through accumulated experiences of change. For example, if the aggregate shown in Table 3-4 reaches 4%, notification of a problem triggers a change management. Causal investigation for analytical

procedures is planned by using the guide form in Figure 3-14b based on complexity, accuracy, generality, and sustainability. If no problem is observed in these views, but it is revealed that sensitivity of the analytical method is insufficient, the guide form in Figure 3-14b will be revised to add sensitivity as a new investigation point. Even when change experiences are insufficient, change management training against assumed accidents can also trigger improvement in the guide forms. This is the improvement of transaction methods explained in Figure 2-2.

Clearly defined business process supports the preparation of appropriate engineering standards to realize smooth implementation of change management. In this section, some guide forms are explained as examples of engineering standards. Formalization of investigation items is easy so long as the scope of activity is limited. Watts (2012) emphasized that the information required on the request for change should be limited and kept simple. A form and form instructions that indicate activities must be prepared to be completed by the requester. He also showed that the temptation to add more information than that identified as essential features should be avoided. Currently, some industries prepare a general form to record various change cases. This sometimes leads to excessive and high context documentation. Simple and deictic guide forms can be prepared on the basis of the activity model, because the scope of a form is well-defined for each activity. Guide forms that are prepared for possible patterns in problem notification, causal investigation, change proposal, and risk assessment occur in each activity of the model and enable smooth changes in management and decision making. Ideally, it is preferable to prepare guide forms for all activities and steps in the model; however, this requires much time and a large amount of resources. Nevertheless, the process can be started by applying it to a group of activities in which information transaction errors occur frequently and then expanded to other groups.

An activity model-based change management system can record decision making among overall activities. Step-by-step decision making process can be traced because the information is stored on a structured activity model. This information warehousing system with related activity model supports information retrieval and utilization in response to the demand by each activity. Some published methods are available for designing detailed systems to warehouse and search such information (Hailemariam, 2010a, 2010b).

3.3.6 Cases analysis

The 86 change cases, which were carried out in a pharmaceutical company in 2010-2012, were analyzed on the basis of the most up-to-date activity model. During the case analysis, addition of activities and model adjustment were required only twice. Firstly, activity A33 and A43 were added to clearly define the function of preparing documents, materials, and human resources prior to implementation. Secondly, recipe development for drug product was separated into two activities of A345 and A346 to clarify functions of design formulation itself and formulating procedures. With these only twice modifications, all cases could be expressed on the activity model. The model after the minor modification was capable of describing the actual industries' change management. This showed that the written reference model is appropriate to handling actual business processes.

We compared the changes which were analyzed on the activity model with the written records of the changes implemented without activity model-based approach. It was checked whether the information was transacted between the four stages of design recipe, design facility, operation, and maintenance. Actually, detailed analysis should be performed to investigate whether the information is transacted to the specific activity which needs to be informed. In this study, we limited to check information transaction between the stages. Because, in the pharmaceutical company, it is implicitly known that information transaction between these stages can be a bottleneck while information dissemination under the stage tends to be successful. In Table 3-6, if information is served from the triggered stage (information provider) to another stage (information accepter) in the activity model-based reanalysis, a point was added to the denominator score in the column of information accepter stage. On the other hand, if information transaction was confirmed on the written record, a point was added to the numerator. The number of cases triggered from design recipe, design facility, operation, and maintenance were 8, 4, 46, and 15, respectively. And 13 cases of top-down type change, which contained introduction of new regulation and sweeping reorganization, were recorded and they were categorized as external. Some examples are listed in Table 3-7. Comparing the total number of information transactions, 130 flows were found by using the activity model based approach, while 104 flows were recognized in the written records. This observation showed that 25% of information transaction is lacking in the written records, which can be covered by using the activity model-based approach. Lack of information transaction would cause recurrence of similar problems in the same division. Actually, some cases of recurrence were contained in the 86 cases.

Although information was well served to the operation stage, lack of information transaction from production stage to design recipe and design facility stages was observed. This shows characteristic of manufacturing industries that change information to produce a product is served naturally, but information on corrective and preventive actions for malfunctions occurring in production is unintentionally left unattended, failing to give feedback to the activities laid upstream of development sequence (i.e. design recipe and design facility). This characteristic prevents cooperation of recipe design, facility design, and production, which is important to achieve sound LCE. As explained in Section 1.3, current computerized applications cannot support this cooperation because they are not based on predefined business processes. It is shown that the activity model-based approach could support this cooperation. Sufficient communication was achieved for change processes triggered by external management, because top-down type management controlled collective notification. Change management system on the basis of the activity model supports comprehensive communication to decrease the risk of accidents caused by the negligence of information transaction. In addition, required time for discussion could be reduced by using the activity model. Relationship of activities, if it is explicitly written down, could promote smooth decision making.

Table 3-6 The number of information transaction between two activity stages. If information is served from the triggered stage (information provider) to another stage (information accepter) in activity model based reanalysis, a point was added to denominator score in the column of information accepter stage. On the other hand, if information exchange was confirmed on the written record, a point was added to numerator. Meshed column shows that the score ratio is not more than 75%.

Trigger stage (Information provider)	The number of cases	Information accepter			
		Design recipe	Design facility	Production (Operation)	Production (Maintenance)
Design recipe	8		3 / 3	8 / 8	4 / 4
Design facility	4	1 / 1		2 / 2	1 / 2
Production (Operation)	46	11 / 20	13 / 18		15 / 19
Production (Maintenance)	15	0 / 2	3 / 6	7 / 7	
External	13	7 / 8	6 / 7	13 / 13	10 / 10
Total	86	104 / 130			

Table 3-7 Examples of change cases.

Triggerd by	Examples of cases
Design recipe stage	Change of calculation formula to adjust conductivity of load solution for a chromatography
	Change of filling bottle
Design facility stage	Change of position of chromatography system to expand working space
	Addition of safety valve on a piping
Operation stage	Addition of sensors to monitor incubation temperature for alarm notification
	Change of operation program of bioreactor to control flow rate of drain
Maintenance stage	Installation of in-line analytical device to monitor cleaning efficiency
	Change of monitoring criteria to control cold room temperature
External change	Change of standard of bioburden to comply with EU-GMP
	Temporal change of freezer monitoring procedure during unscheduled blackouts

An example of change cases is explained as follows. The case indicated that fluctuation of dissolved oxygen concentration in production culture was settled by changing control parameters (Figure 3-15). In the written document, this change was not notified to recipe design stage. It had to be notified to update the operability information in Table 3-4 from 50±15% to 50±5%. Due to this notification failure, process characterization study was planned to test the effect of oxygen concentration within unreasonably range of 20–80% which is too wide against ±5% of updated operable range. Some good recipes were unreasonably rejected to avoid the unlikely risk of fluctuation of oxygen concentration. Although some people may criticize that it is caused by insufficient personal management, it is actually difficult to make correct decision of dissemination by only personal contemplation without guide forms. Handling this case on the activity model and guide forms, the problem of oxygen concentration fluctuation could be notified from activity A54: Manufacture pharmaceuticals to activity A51: Manage production via activity A56 and A57. Notification form from the activity A54 is shown in Figure 3-16a. The manage activity A51 can judge where the information should be notified by referring enumerated activities in Figure 3-16b. The activity A2 can make the plan to investigate the effects of operability improvement on procedures of process characterization study as Figure 3-16c. In section 4.3.3.2, process scenario showing causal relationship from oxygen concentration in production culture to quality attributes in downstream step will be explained. Appropriate change management of a control parameter is consequently related to product quality management.

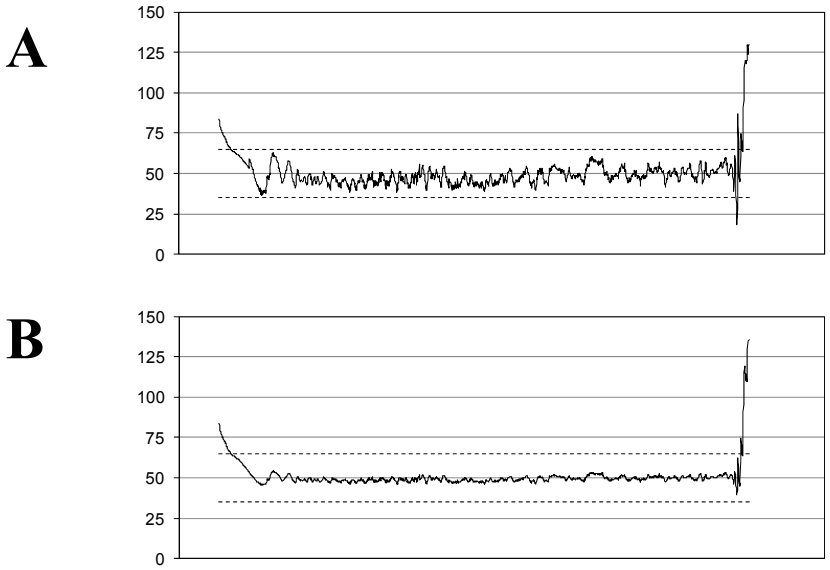


Figure 3-15 Operability improvement of dissolved oxygen concentration control in production culture. A: Before change of control parameters, B: After change. Broken line indicates predetermined control limit shown in Table 3-4.

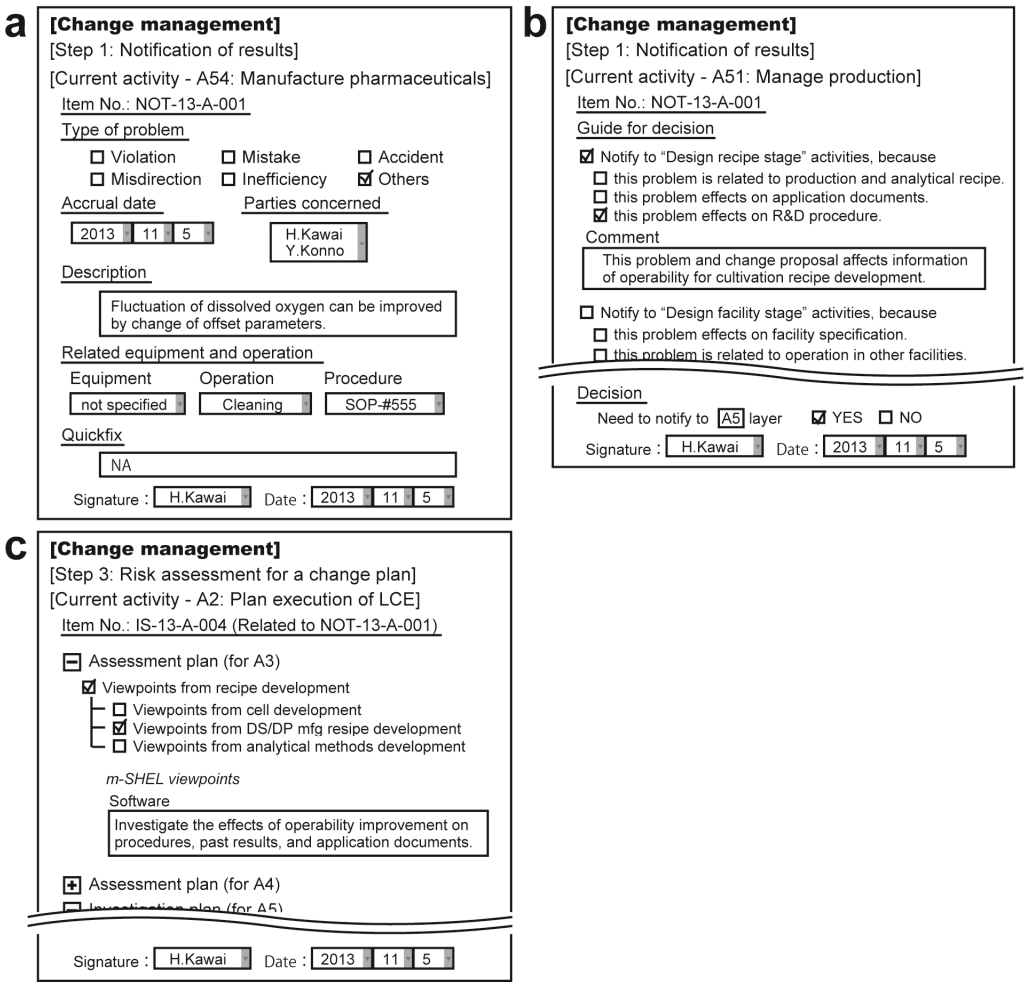


Figure 3-16 Guide forms for notification of a problem in A54 (a) and A51 (b) and for risk assessment for a change plan in A2 (c).

The activity model was redesigned and new functions were defined through case analysis. Improvement of transaction schemes explained in Figure 2-2 is triggered by redesigning of the model. At the beginning of case analysis, activity A355 was "Develop formulation of drug substance and drug product." This activity only defined the function to develop formulation, packaging, and labels of drug substances and drug products. The model lacked the function to develop formulating and filling procedures of drug product (e.g., procedure to mix drug substance with formulation buffer, procedures to fill drug products). A case of changes indicated that a filling device was changed to different mechanistic one because insoluble aggregates were generated by shear stress on sliding surface of the previous device. In R&D team, filling methods was not investigated sufficiently. The team did not recognize the risk of shear stress on causing insoluble aggregates until drug products were produced by using the commercial device. In initial activity model, the activity to investigate filling methods was not defined. Therefore, "A355: Develop formulation and filling vessel and package of DS/DP" and "A356: Develop recipe of formulating and packaging process" were newly defined to clarify functions of formulating methods as well as designing formulation (Figure 3-17). Guide forms like Figure 3-13d and Figure 3-14b were then designed. Decision making of Manage activities is supported by these new guides built in the activity model. In current industries, this improvement is occurred among a limited number of personnel who experiences failures. In contrast, activity model-based management can generalize the experiences by reflecting them in the activity model.

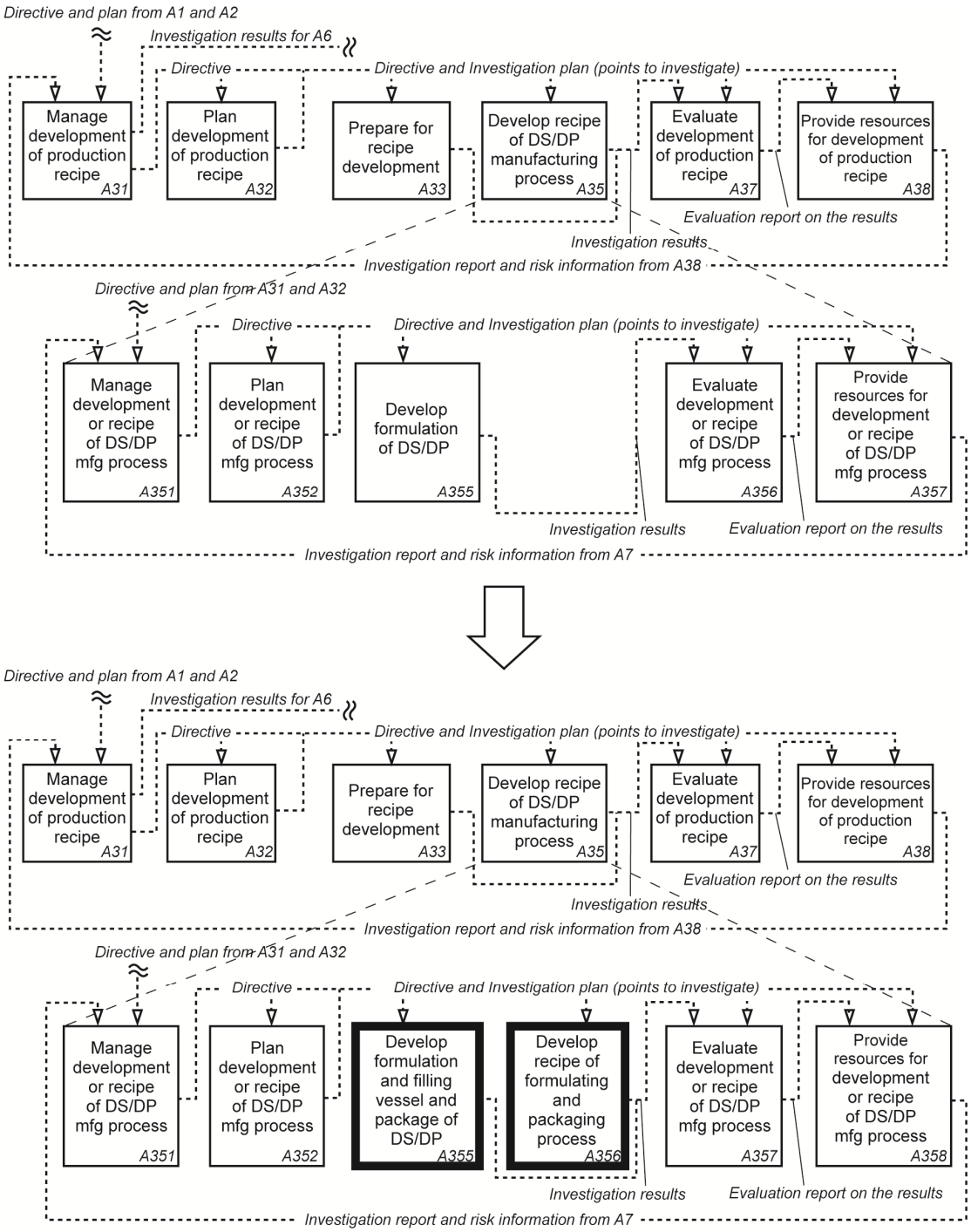


Figure 3-17 Definition of new function through remodeling on the basis of a case analysis. Activities with bold line were newly defined.

3.3.7 Summary

The protocols are defined in order to record the decision making process which are otherwise hanged on a personal memory. These records enable to handle change cases smoothly by tracing similar cases in the past. For example, when introduction of new

equipment into a certain factory is planed, smoother implementation would be made possible by tracing similar decision making process already experienced, even though the person in charge who memorizes past implementation is not present. The decision making processes are recorded on the guide forms which are prepared on the activity model as engineering standards. Continuous improvement of the guide forms by accumulating decision making experiences and improving defection in the past decision becomes possible. Appropriate decision for information handling supports cooperation of recipe design, facility design, and production stages to achieve sound process LCE. Individual frameworks and methodologies to prepare items in each guide form are available as PQCDSM framework, m-SHEL model, and 4M-4E. Meanwhile, this study focused on how the products obtained by the frameworks are integrated together. The activity model-based approach integrates various management tools and frameworks so as to achieve a series of sound overall business processes.

Applicability of this approach is demonstrated by change cases analysis in an actual company. With only two minor modifications, 86 cases could be expressed on the activity model, showing the model was sufficiently applicable to actual industries' change management. Information was well sent to the operation stage, while negligence of information transaction from production stage to design recipe and design facility stages was observed. While lack of necessary information transaction is able to be prevented by using the activity model-based approach, a supporting system for information transaction between production and design recipe is necessary.

3.4 Conclusions

In this chapter, pharmaceutical process LCE was unambiguously arranged into hierarchical activity stages by using the IDEF0 engineering activity model. This model frames the hierarchical activities of first the Define desired product performance stage, second the Design product stage, and third the three subordinate stages: Design recipe, Design facility, and Produce. This hierarchical structure represents functions of administration, coordination, and implementation. To facilitate LCE implementation, horizontal PDCA occurring on each function and vertical PDCA occurring between the hierarchical functions facilitate LCE implementation are defined. By designing business process management systems based on the activity model, thorough and bias-free handling of information can be realized. Protocols to produce outcomes, such as quality target product

profile sheets, critical quality attributes assessment lists, process parameters risk assessment results, and production control charts, are redefined functionally on the activity model with associated business processes.

If a problem occurs in LCE implementation, change management must be triggered. The change management is described in the activity model. Decision making, which is otherwise based on personal memories, is recorded on engineering standards (such as guide forms) which are prepared on the activity model. Continuous improvement in the engineering standards becomes possible by accumulating decision making experiences and improving defects in past decisions. Effectiveness of the change management approach was demonstrated using cases analysis from an actual company. After only twice minor modifications, 86 cases could be expressed on the activity model, showing that the activity model-based approach is sufficiently adaptable to use in actual change management situations. Information was well served to the operation stage, whereas negligence of information transactions occurred from the production stage to the design recipe and design facility stages. While negligence of necessary information transaction can be prevented by the activity model-based approach, additional supporting systems are needed for information transactions between production and design recipe stages. In the next chapter, we propose a Quality-HAZOP system to support causal investigations and exchange of risk information between the design recipe and production stages.

In current pharmaceutical industries, a limited number of experts still determine the business process and related procedures such as committee structures, responsibility systems, and outcomes. We illustrated the business process of pharmaceutical process LCE in an activity model and proposed activity model-based management for pharmaceutical process LCE. This activity model-based approach supports a wide range of business processes beyond the walls in different projects, different development phases, and different business organizational structures, and thus facilitates a holistic and proactive LCE implementation for continuous improvements in quality.

4 Supporting System for Practice

4.1 Introduction

In the Section 3.3.6, analysis of past change cases showed that information obtained in the Produce stage is unintentionally left from giving feedback to activities that are upstream of the development sequence (design recipe and design facility). This suggests there is a barrier against information transactions between the three implementation stages of Design recipe, Design facility, and Produce stages defined in the Section 3.2.3. Usually, knowledge of both product-specific processing behaviors obtained in the recipe design activity and equipment/operation/material-specific processing behaviors obtained in facility design and production activities are concurrently developed throughout the lifecycle of a pharmaceutical product, as shown in Figure 2-1. Information on product-specific processing behaviors includes the enterprise-level requirements of processing behaviors and is independent of specific knowledge of manufacturing equipment (e.g., effects of range of fermentation temperatures on production rates; effect of range of chromatography pH on product variants). This information is usually developed in laboratories knowledge of both chemistry and processing requirements; this corresponds to the design recipe stage. In contrast, information on equipment/operation/material-specific processing behaviors contains specific knowledge about manufacturing equipment and operation (e.g., durability and accuracy of a temperature probe in a bioreactor; pH fluctuation levels of a chromatography skid). This information is developed to aid manufacturing in a plant. Information on equipment structure and specifications derives from the Design facility stage. Information on operational processing results derives from the Produce stage. To implement pharmaceutical process LCE, it is necessary to integrate information on both product-specific processing behaviors and equipment/operation/material-specific processing behaviors (Nasr, 2007; Yu, 2008).

Improvements in the quality of industrial products and processes require collection and analyses of data to solve quality related manufacturing problems. To facilitate the management and transfer of large amounts of complex data, as well as information and knowledge during the lifecycle of a product, an intelligent informatics framework is required (Zhao *et al.*, 2005). While quality improvement programs such as six sigma, design for six sigma, and *kaizen* encourage collection of data to solve quality problems, with advances in automation and computer systems, data from manufacturing processes is becoming more and more available (Koksal *et al.*, 2011). Previous studies discuss process development methods ranging from product design to production (Rathore and Mhatre, 2009; Lepore and Spavins, 2008). Although these studies can guide the design of a reasonable process, they do not specify a complete implementation of the continuous lifecycle improvement of the process. For several decades, chemometrics has been studied in pharmaceutical quality analysis (Fisher and Jones, 1987). Statistical methods such as analysis of variance (ANOVA), principal component analysis (PCA), and partial least square (PLS) have been proposed to predict the likelihood or root causes of deviations in quality (Wu *et al.*, 2011; Huang *et al.*, 2009; Huang *et al.*, 2011; Gunther *et al.*, 2009; Gilabert *et al.*, 2004). Other methods, which model a process without solid rationale, have been studied, such as soft-sensors (Warth *et al.*, 2010; Soons *et al.*, 2008) and neural networks (Wu *et al.*, 2011; Behzadi *et al.*, 2009). These individual methods are useful in determining a possible scenario to explain deviations in quality from specific data. However, Doherty and Lange (2006) have warned about chemometricians that slip into self-complacency. Fairly or not, chemometricians are often seen as divorced from reality, spending endless time in their ivory towers developing and fine-tuning models that have no practical use. It is extremely important that industrial chemometricians have practical process knowledge and good working relationships with process chemists and engineers.

Purdue University introduced systematic approaches to describe operational knowledge on the basis of hazard and operability studies (HAZOP) (Srinivasan *et al.*, 1998a, 1998b; Viswanathan *et al.*, 1998a, 1998b). These approaches focused on describing operational behaviors. In today's pharmaceutical industries, there are effective methodologies for risk analysis and risk description. However, they can be improved only on the basis of a system that allows exchange of risk information. For continuous process LCE, it is necessary to build a risk information transaction system that disseminates a finding in the manufacturing results to trigger further research in the surrounding logic and that improves

process control strategies by connecting the rationale to operational risks. A perspective on this concept was introduced by Gernary *et al.* (2012).

While data mining methods based on various statistical analyses can certainly trigger deeper understanding of process behavior, a business process to catch the trigger and disseminate the understandings among recipe design, facility design, and produce stages is necessary in order to promote more effective use of a finding. We focus on designing a knowledge-based risk information transaction system between recipe scientists and process engineers. In this chapter, we first define process behaviors for the purpose to describe process scenarios developed by LCE activities in pharmaceutical industries. Second, we propose two scenarios for representing a process that can lead to a quality hazard: one is a process deviation scenario that does not contain specific information on equipment, operation, or materials, and the other is a procedural control scenario that contains specific information on them. We also propose a system called Quality-HAZOP to show that the overall pathway from manufacturing errors to deviations in product quality; the pathway is described by integrating the two scenarios. Third, we introduce a case-based reasoning approach to find relationships between operational deviations written in the procedural control scenario.

4.2 Proposed Structure of Production Process

4.2.1 Introduction

Definitions of process elements and deviations differ among guidelines and companies (PDA, 2013). Even within a same company, the definition that describes a process could differ across individuals and organizations. Such differences in definitions seem to be caused by differences in the scopes with which words are used. For example, recipe scientists, process engineers, and quality assurance personnel describe a process from the points of view of identifying chemical or biological relationships between parameters, improving controllability by setting appropriate operational parameters, and effects on quality and systematic documentation, respectively. Although unifying meanings of the terms is an important issue, we do not focus on it. Instead, we define process elements and deviations for the limited purpose of describing process scenarios developed by LCE activities in pharmaceutical industries. Some guidelines (PDA, 2013; CMC Biotech Working Group, 2009; ICH, 2000) only describe production process structures from the point of view of recipe design rather than from the viewpoints of design facility and production. In addition,

they only define input and output parameters; however, such definitions lead to operational cause and effect relationships being confused with process behavioral ones. Previous studies (Rathore and Mhatre, 2009; CMC Biotech Working Group, 2009; Garcia, 2008) describe process understanding as knowing design space of several process behavioral inputs that affect outputs. While this is an important aspect to understand a process, clarification of detailed operational relationships is another important aspect. Therefore, we intend to describe relationships that include not only process behaviors but also operational elements.

4.2.2 Classification of Operations and Behaviors

We classify the elements in a pharmaceutical process as in Table 4-1 and divide a production process into a frame of structured process operations and behaviors as in Figure 4-1. A process consists of several process stages as defined in ISA-88 (1995) (Figure 4-1a). The process stages can be arranged in parallel or sequence. Some attributes in one process stage are provided as input to the next process stage (solid lines in Figure 4-1a). Raw materials are provided to all process stages as input (broken lines in Figure 4-1a). A process produces product from raw materials via several process stages. The process elements that represent operations and behaviors in a process stage are schematically shown in Figure 4-1b.

Input parameters include *material attributes* and *adjacent inheriting attributes*. The attribute here does not mean only the measured value of a parameter but also a testing and evaluation results compared with predetermined limits, normal fluctuating ranges, and the intuition by experts. Material attributes are specific properties determined by material acceptance tests and vendor certificates (e.g., result of testing for moisture content in a powder reagent, pH of a reagent obtained by compendial testing). Although accurate adjustments of material attributes are impossible, criteria of acceptance tests can be applied to control their properties within desirable ranges. Adjacent inheriting attributes are the outputs from the previous process stage. Both quality and non-quality aspects are included in the attributes. For example, for the consecutive chromatography stage-A following stage-B, states of product variants and impurities in the pool solution of stage-A can be the adjacent inheriting quality attributes for stage-B. On the other hand, the pH in the pool solution of stage-A, which does not directly reflect a quality aspect, is an adjacent inheriting non-quality attribute. These input attributes are provided to a process stage and affect process behavior. Since the input attributes are determined outside of the process stage, they are uncontrollable by the process stage.

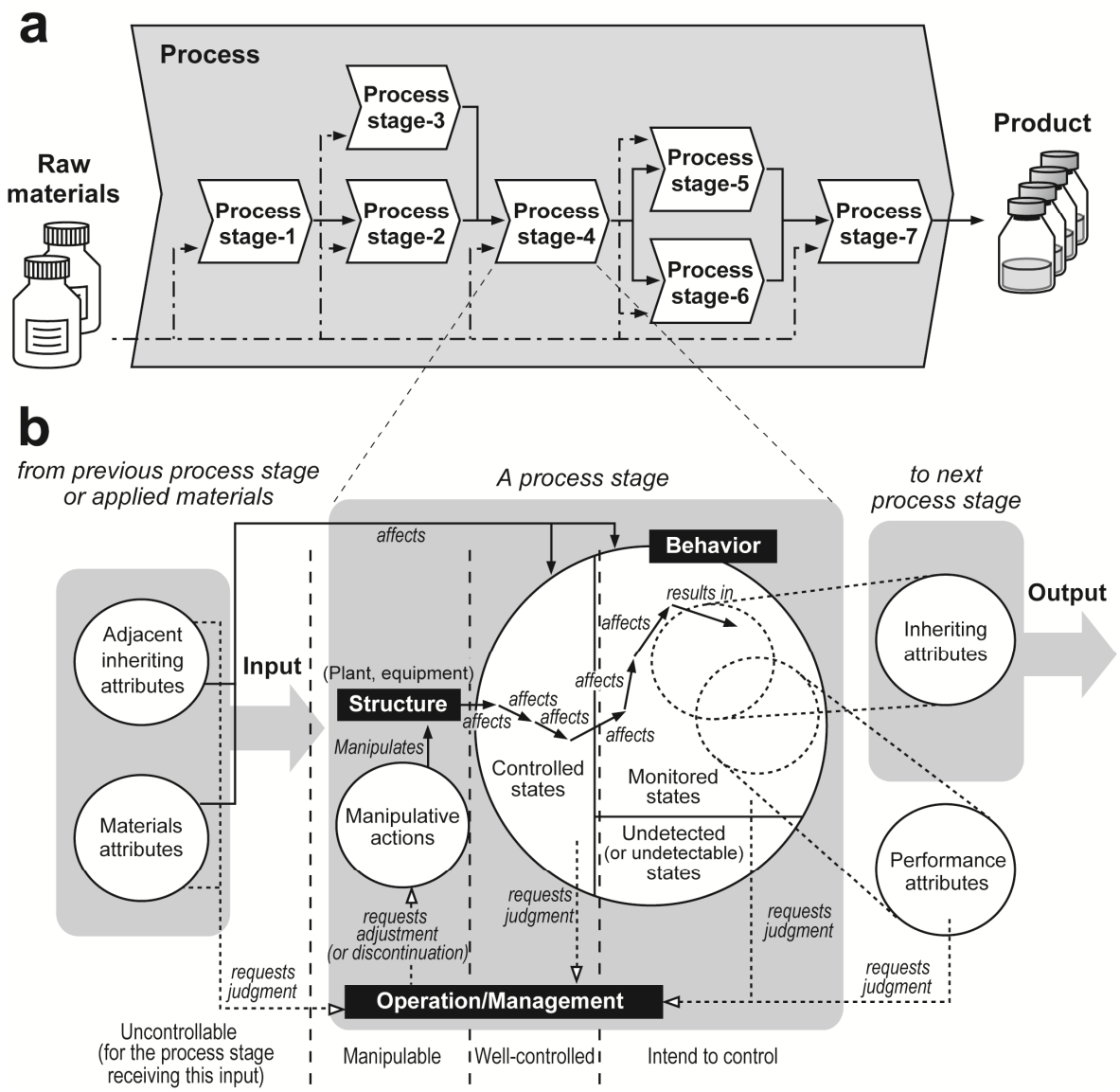


Figure 4-1 Frame of a set of structured process operations and behaviors. a: A process consists of interconnected process stages. Solid arrows show the interconnection of paired process stages. Broken arrows show input of raw materials. b: Structured process operations and behaviors. Solid arrows show relationships between elements. Dotted arrows show information transactions that trigger a decision making to adjust manipulation.

Table 4-1 Classification of process elements.

Parameters	Description
Process input	
Material attributes	Material properties provided by acceptance tests and vendor certificates. The criteria of acceptance tests control their properties within desirable ranges.
Adjacent inheriting attributes (Adj-IA)	The output attributes provided from the previous process stage as inputs.
Operational actions and behavioral states	
Manipulative actions (MA)	Individual operating actions in specific manufacturing equipment. These actions are manipulated to achieve robust and reproducible operations by set point, manipulation range, and equipment maintenance criteria.
Controlled states (CS)	Well-controlled states directly controlled by manipulative actions. These states must be controlled within predetermined limits to ensure product quality.
Monitored states (MS)	These detected states are tested for intermittent process monitoring and remain inexactly controlled.
Undetected states	These are undetected because of impracticality, impossibility, or misapprehension.
Process output parameters	
Inheriting attributes (IA)	The attributes continued in the next process stage as adjacent in-process inheriting attributes. Testing of certain quality or non-quality factors in a process stage for checking effects on next process stages. Critical quality attributes and other attributes, which directly affect product quality, are included.
Specifications of product	Tests with associated acceptance criteria conducted on a set of product quality attributes at final lot release.
Process performance attributes	
Performance attributes (PA)	Testing of certain states in a process stage for checking performance to satisfactorily achieve the intended product quality and process consistency.

In a process stage, *manipulative actions* are defined as individual operations by specific manufacturing equipment (e.g., valve opening action to a level of speed, setting action on pump speed, setting action on values of proportional integral derivative controller of reactor's temperature). These actions achieve robust and reproducible operation by giving appropriate set points (e.g., pump speed at 60 Hz), manipulation ranges (e.g., pump speed within ±5 Hz), and equipment maintenance criteria (e.g., ±3 Hz of calibration criteria for pump frequency, replacement frequency of pump bearing) to the manufacturing equipment. Plant operators can almost perfectly perform such actions according to their wishes, so long as no error and malfunctioning occur. Manipulative actions (*operation*) applied to equipment

(*structure*) holding matter (solutions, reagents, gases, etc.) of the input attributes results in sequences of states (*behavior*). This framework to represent a process in structural, behavioral, and operational aspects is known as multidimensional formalism (Batres *et al.*, 1999).

Process behavior is represented by a set of *controlled states (CS)*, *monitored states (MS)*, and *undetected (or undetectable) states*. The propagation of controlled states can be determined with specific knowledge of equipment. In contrast, the states from a controlled state to monitored process states can be expected without specific knowledge of manufacturing equipment and can be equally treated in laboratories and manufacturing plants. Controlled states are directly controlled by manipulative actions (e.g., state of flow rate in a chromatography skid, state of temperature of cell cultivation, state of dissolved oxygen concentration in cell cultivation). A result of the controlled state causes following states. It would be ideal to control all behavioral states at will, but most often some states remain uncontrolled or only partially controlled. Therefore, industries try to put them within some acceptable ranges though manipulating the controlled states.

Some states are undetected because they do not need to be monitored. Other states should be monitored but cannot be monitored because of inadequate technologies or theoretical impossibilities. Sometimes, they are not monitored because manufacturers are unaware of their importance. Technological innovations can change detectability. Accumulation of process understandings may motivate manufacturers to notice the importance of an undetected state. It is necessary to comprehend relationships between the newly detected states found by the advancement of knowledge and other states. Such updated information about the relationships triggers improvements in the controllability of equipment, operating procedures, and monitoring items and criteria. The quality by design approach and process analytical technology concept aim at efficiently using such new knowledge to improve overall process controls.

The performance of a process stage is evaluated based on some monitored states. The representative of them is *performance attributes (PA)* (e.g., testing results of product variants, impurities, and pH in the pool solution; results of yield and elapsed time of the process stage). These performance attributes are tested to determine whether or not they satisfy predetermined limits; such tests facilitate monitoring of intermittent process stages. Monitored states that are not designated as process performance attributes are just for monitoring propagating states (e.g., testing results of lactate concentration and osmolality in a

production culture stage, which *may* affect final cell viability). These states that are outside of lot release testing are used for intermittent process monitoring, and process behavior is described with these states. Process understandings are deepened by describing this process behavior in a written scenario.

Outputs from a process and/or a process stage include *specifications of product* and *inheriting attributes (IA)*. Specifications of product are test results on the final product (e.g., testing results of aggregates and host cell protein in the product). Acceptance criteria are set to assure the quality of the product to be released (e.g., no more than 5% of aggregates). The specifications are defined as the final output of a process. Some states in a process stage are inherited by the next process stage as inheriting attributes. A set of inheriting attributes is not always a subset of performance attributes. For example, in a chromatography step to control aggregates and fragments of product, the contents of the aggregates and the fragments should be performance and inheriting attributes at the same time. On the other hand, contents of glyco-variants may not be the performance attributes but the inheriting attributes. In a production culture step, product concentration in the culture and final cell viability would be the performance attribute and inheriting attribute, whereas osmolality, which is not controlled in the culture but directly affect next step, may not be the performance attribute but the inheriting attribute. Yield and elapsed time, for example, are process performance attributes, but they are not inheriting attributes.

4.2.3 Deepening Process Understanding

In general, a process design is started by determining required levels of values for a set of performance attributes. In the early stage of process design in pharmaceutical industries, the required levels for some performance attributes cannot be clearly determined, because information from preclinical and early clinical studies is insufficient as explained in Section 2.2. Therefore, requirements for process performance as well as chemical or biological relationships between controlled and monitored states are deepened as product development progresses. Information about relationships between behaviors is progressively accumulated during R&D in laboratory and manufacturing practice. On the basis of such information, ranges on the controlled states are determined so as to achieve the required levels of performance attributes. Finally, manipulative actions are determined to realize the required ranges on the controlled states. Manipulative actions are adjusted by monitoring both input

attributes and behavioral states so that the performance attributes satisfy predetermined acceptance criteria. Process management function determines the optimal manipulative actions based on the judgment requests triggered by the monitoring results (Figure 4-1b). Sometimes, the management function judges discontinuation of manufacturing. If the states are still controllable, manipulative actions can be changed within permitted ranges to satisfy the criteria on process performance attributes. This approach to ensure final product quality by designing, analyzing, and controlling manipulations through timely measurements of critical attributes is known as the process analytical technology (PAT). To determine optimal actions, relationships between operations and behaviors must be explicitly described. As explained in Section 4.2.1, current studies of LCE implementation as well as some guidelines focus only on process behavioral aspects. Concepts of quality by design, design space, and process analytical technology basically cover overall process control and management not only in behavioral aspects but also in operational and structural aspects.

4.2.4 Definition of Deviations and Failures

Chi-wan Chen outlined the U.S. Food and Drug Administration's view of quality by design and abstracted key elements as follows (Arnum, 2007): A pharmaceutical product profile is targeted, and then, product's critical quality attributes befitting the profile are determined. To satisfy the acceptance criteria of the product's critical quality attributes, the in-process critical/key performance attributes must satisfy a specified range. To this end, the critical/key controlled states must be controlled within a certain range. The ranges of performance attributes and controlled states are determined through the product quality lifecycle implementation (PQLI) approach (Lepore and Spavins, 2008; Garcia et al. 2008; Davis et al., 2008; Rathore, 2009).

Although the concept of PQLI provides a basic scheme of process development, there is still a gap between a recipe scientist and a plant/process engineer because the points of focus in process states are different between the two persons. As shown in Figure 4-2, we describe the relationship between control ranges of process states. The manipulative actions can be adjusted within desirable ranges of fluctuation so that the controlled states satisfy the normal levels. Although the material attributes are not described in the Figure 4-2, they are also tested to satisfy acceptance criteria before use. During recipe R&D activities, process characterization studies are performed to define design space within a knowledge space. This

knowledge space is expanded by the accumulation data from repeated manufacturing batches as well as process characterization studies. The knowledge space only contains information regarding regions that have been investigated, and the design space defines the region in which an acceptable product can be produced. The characterized range and acceptable range for product specification, performance attributes, and controlled states are determined from the knowledge space and design space, respectively. It is also checked that test results of the monitored states satisfy normal range. If a monitored state is characterized to affect quality or process performance, it is redefined as performance attribute. Manufacturing is performed to meet the acceptable range, and the results vary within a normal range. On the basis of recipe R&D results, process control limits are established for manufacturing. A rejection limit is set as the upper and lower limits of the acceptable range defined by the design space. Alert and action limits can be set to monitor or control out-of-trend results. Even if a manufacturing result satisfies the acceptable range, causes and quality effects have to be investigated when the result deviates from the alert or action limits. These limits and a set-point of controlled states are designed to satisfy the limits of product specification and performance attributes. Controlled states are controlled within acceptable limits by adjusting manipulative actions within expected ranges.

In this study, deviations are defined as the results of performance attributes or product specifications being out of limits. Out-of-trends of monitored states are also considered as deviations because they indicate an abnormal situation occurs even if they are outside of lot release testing. Out-of-limits controlled states are defined as process state failures, whereas an inappropriate manipulation is defined as an error. Not only the final product testing but also the in-process control is a factor that defines product quality in the quality by design approach. Therefore, a quality hazard is defined as a condition where a deviation or a process state failure occurs. Recipe scientists generally focus on the relationship between deviations and process state failures of product specifications, performance attributes, monitored states, and controlled states. On the other hand, plant and process engineers focus on the relationship between failures of controlled states and manipulative actions. There is a gap between the views of scientists and engineers, so that previous assessments of the overall process were inapplicable. Therefore, we construct an integration system of these different views.

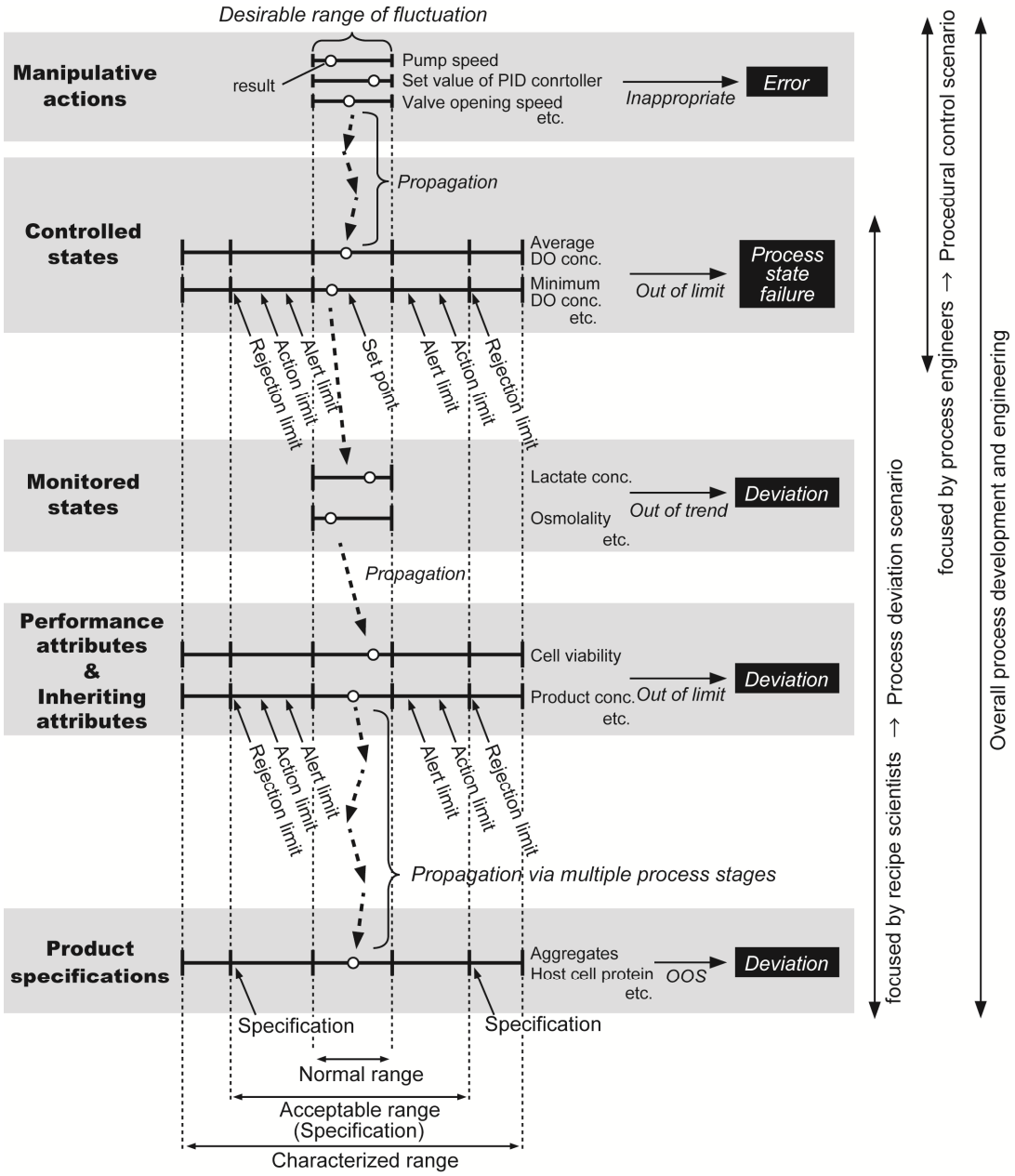


Figure 4-2 Relationship between process operation and behavior. DO: Dissolved oxygen, OOS: Out-of-specification.

4.2.5 Hierarchical Description of Process Deviation Relationship

The relationship among deviations and process state failures become clearer with the progression of recipe R&D. This relationship is described in the process deviation scenario for each process stage. This scenario is developed in Node-A3: Develop production recipe. This scenario is the model used to represent process behavior hierarchically. The hierarchical relationship among product-specific processing states can be presented as shown in Figure 4-3. This figure shows the sequence from raw materials to a product through a process. Sequential process stages constitute a process. The sequence of process stages may be

branched (e.g. production culture stage continues from the pre-culture and media preparation stages). To compile this scenario, process state failures of controlled states or deviations of adjacent inheriting attributes are first written as inputs for each process stage. Next, resulting deviations are written as internal propagations, and the results of the propagations are written as outputs. In the case where not less than two simultaneous deviations result in a deviation, all routes from the deviated items are connected. In the case of deviation in the rejection limit, no route is connected to the next item. Deviation of an inheriting attribute must continue in the next process stage as deviation of the adjacent one. On the other hand, deviation of a performance attribute which is not designated as an inheriting attribute does not continue in the next process stage. Not only monitored states but also performance attributes can be written as internal propagation because the scenario that a performance attribute affects another performance attribute is possible. For example, in biopharmaceutical production culture stage, cell viability defined as performance attribute affects host cell protein content defined as another performance attribute. The hierarchical relationship diagram in Figure 4-3 covers recipe scientists' view rather than plant and process engineers' view. In the next section, we describe the plant and process engineers' view in a HAZOP-based scenario and propose a system to bridge the two views.

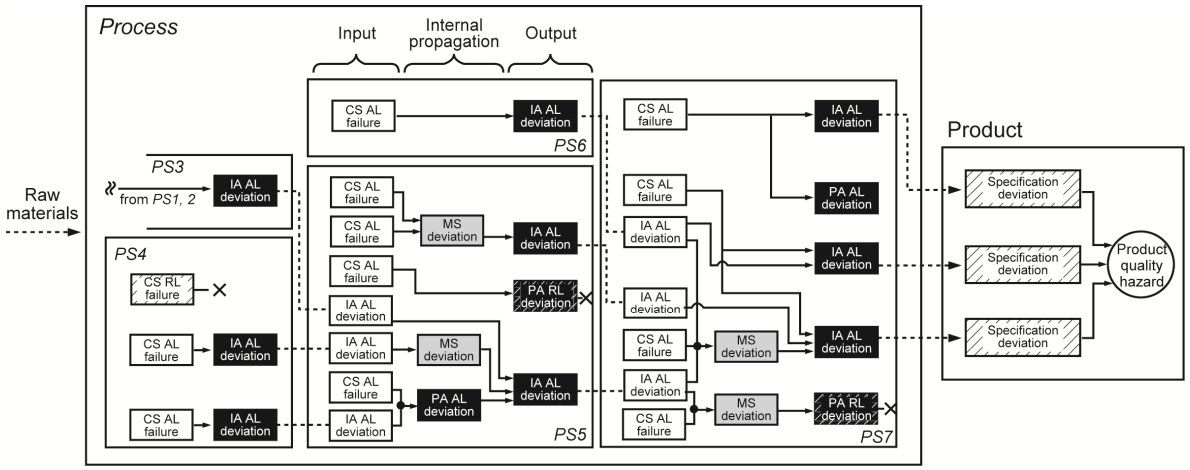


Figure 4-3 Process deviation relationship diagram. White box: a process state failure of a controlled parameter (CS) or deviation of an adjacent inheriting attribute, gray box: a deviation of a monitored state (MS), black box: a deviation in an inheriting attribute (IA) or a performance attribute (PA), a box filled with a diagonal pattern: a rejection limit failure or deviation. PS: process stage, AL: action limit, RL: rejection limit.

4.2.6 Summary

In this section, we classified process operations, controls, states, and deviations in the pharmaceutical production process for the purpose of describing a recipe scientist's viewpoint and a process engineer's viewpoint. Specifications, inheriting attributes, performance attributes, controlled states, and material attributes have already been classified in previous studies and guidelines though the names are different. We additionally defined monitored states, undetected states, manipulative actions, and adjacent attributes. The monitored states indicate intermediate states which may bridge the causal relationship between the controlled states and performance attributes. The manipulative actions are defined to distinguish operational inputs and controlled states. The manipulative actions are almost perfectly manipulated according to operator's wishes as long as no errors or malfunctions occur. Operators can control the controlled states in expected range. Previously, since the output and performance index are confused, the results of a process are not clearly described. The inheriting attributes are outputs of process stages; on the other hand, the product specifications are outputs of a process. Performance attributes are defined as performance index to evaluate product quality and process consistency.

Relationship among manipulative actions and controlled states are determined on the basis of operational knowledge specific to equipment. On the other hand, relationship among controlled states, monitored states and performance attributes can be determined independent of manufacturing equipment, so that they apply commonly both in laboratories and manufacturing plants. The relationship between process stages is described by succession of inheriting attributes. This classification is required to illustrate the relationship of overall process elements reflecting process stages' linkage.

We defined the deviation as out-of-limits in product specifications, performance attributes, and monitored states. These variables are controlled so that they fall into a certain range, because tight control of these variables is often difficult. Out-of-limits in controlled states are defined as process state failures. Since the parameters are well-controlled in certain limits, if unsatisfied situations occur, it should be called failure. Unsatisfied manipulative actions are defined as operational errors. Clear definitions of deviations, failures and errors prevent miscommunication in personnel with different scopes. The next section proposes a system to describe the relationship between deviations, failures, and errors by using the defined process elements.

4.3 Quality-HAZOP

4.3.1 Introduction

To facilitate the management and transfer of large amount of complex data as well as information and knowledge during a product's lifecycle, an intelligent informatics framework is required (Zhao et al., 2005). In this section, we develop model-based supporting tools to describe information of phenomenal sequences in process chemistry, independent of plant structural information, and information of propagating events in manufacturing operation, ranging from procedural errors to process hazards. The former information is available across specific plants, while the latter is used for detailed risk analysis of control recipes in a specific plant. We propose a system to represent scenarios reaching a quality hazard from several deviations, failures, and errors. One is a process deviation scenario that does not contain specific information on equipment, operation, or materials, and the other is a procedural control scenario that contains specific information on them. In the previous section, the process deviation scenario is introduced as a system that describes the relationship among deviations in product-specific processing states. In this section, the procedural control scenario is explained. A previously reported system for performing process hazard analysis and accident preventive design for chemical plants (Kawamura *et al.*, 2008; Kitajima *et al.*, 2010) is used to design the procedural control scenario. Although this system enables analyzing the risks for quality and productivity as well as safety in the form of HAZOP, its application is currently limited to safety in chemical industries. We focus on quality risk management, which is a more interesting aspect for pharmaceutical industries. The overall pathway from manufacturing error to deviations in product quality is described by integrating the two scenarios. This system is called Quality-HAZOP. We show that the system enables analyzing the risks regarding equipment, operation, and recipes that could affect product quality. Bidirectional commitment of recipe design and manufacturing functions through the system is elaborated.

4.3.2 Combination of Hierarchical Process Deviation Scenario and HAZOP

A trigger error that occurs in a unit procedure (as defined in ISA-88) propagates to one or several process state failures and consequent deviations. The procedural control scenario describes the propagation process. This scenario is developed in Node-A53: Prepare

for manufacturing and maintenance. Control recipe is determined in this node on the basis of master recipe provided from A3. A trigger error is classified into equipment, operation, and material types. Here, material not only means raw materials but also includes all materials and conditions that are the input from outside of a unit procedure, which contains deviations of adjacent inheriting attributes. The trigger error information includes details of the equipment in which the error occurs, the type of error event, materials used in the equipment, and the probability of the error occurrence. As this scenario describes equipment assignments in detail, this information is defined in a control recipe (as defined in ISA-88). To realize productive and safety production of high quality products in a process, the control recipe consistent with equipment status and structure should be generated (Fuchino *et al.*, 1999). The propagation of an error is written step by step for each sequential device in piping and instrumentation diagram (P&ID) in the form of HAZOP until the propagation results in a process state failure of a controlled state that is defined in the process deviation scenario. In addition, the sensors and analytical devices used to detect propagating events and the countermeasures against the propagation are given with each step. The countermeasures are expressed as layers of defense in accordance with the conventions of AIChE/CCPS (2001) (defense layer-1: Process design; defense layer-2: Basic process control systems and process alarms; defense layer-3: Critical alarms and human intervention; and defense layer-4: Safety instrumented function (interlocking)). When an error occurs, defense layers against propagation can be traced. The indication of activity by possible defenses enables prompt intervention by manufacturing operators and allows investigation of the effectiveness of the countermeasures applied during the propagation. The procedural control scenario is used for risk analysis of hazard preventive designs in manufacturing procedures.

Figure 4-4 shows the schematic illustration of Quality-HAZOP, the system that bridges the process deviation scenario and the procedural control scenario. The process deviation scenario describes the relationship between process state failures of controlled states and deviations in monitored states or performance attributes until a deviation in product specifications occurs. On the other hand, the procedural control scenario describes the pathway of hazard propagation in equipment caused by an error until a process state failure of controlled states, which is defined in the process deviation scenario, occurs. The two scenarios are easily incorporated into Quality-HAZOP by bridging scenarios with the common items in the process state failures. Therefore, the Quality-HAZOP describes the overall pathway from a procedural error to product quality hazards. Since the procedural

control scenario describes how the detectors and defense layers are applied to prevent propagating events, it is possible to manage their performance in case of the events.

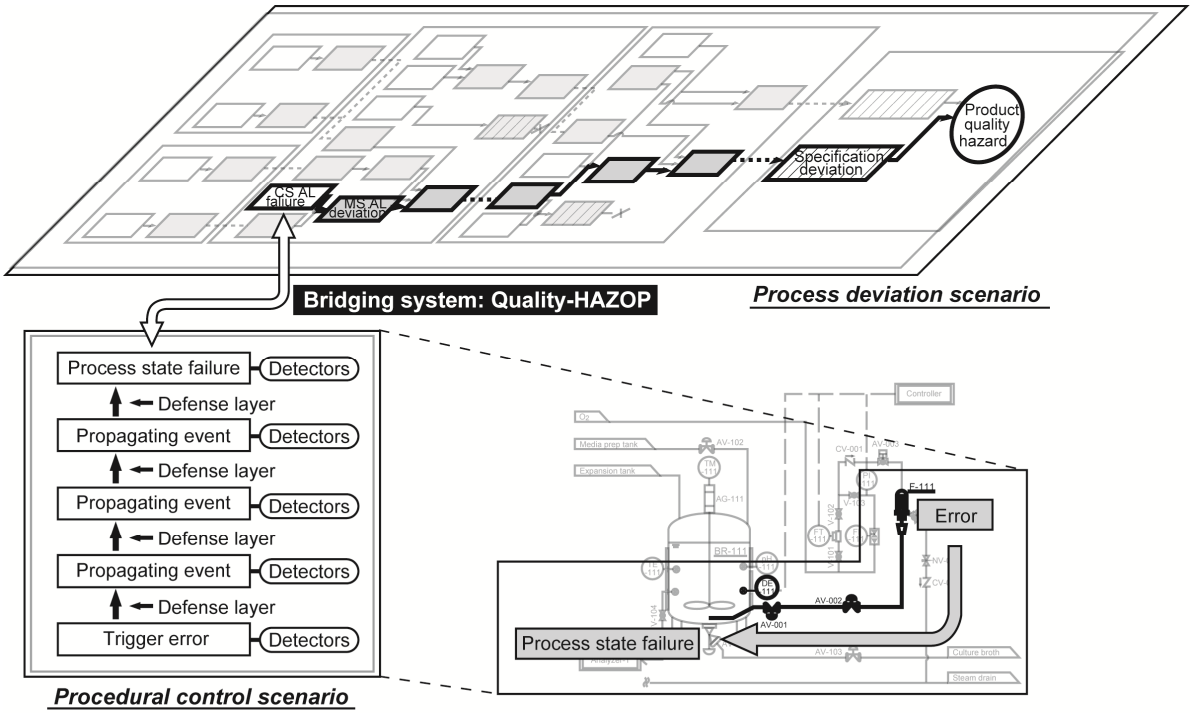


Figure 4-4 Quality-HAZOP system, which bridges the process deviation and procedural control scenarios.

4.3.3 Representation of a Biopharmaceutical Production Process

4.3.3.1 Addressed Process

Aksu et al. (2012) showed that the role of LCE is markedly more critical in biopharmaceutical products owing to the inherent poor stability compared with conventional low molecular weight products. There is greater uncertainty in biotechnology manufacturing because it involves both complex products and processes. Some level of product and process knowledge obtained by LCE is generally necessary for such complex products and processes (Rathore and Mhatre, 2009). In this study, Quality-HAZOP is applied to a biopharmaceutical production process. Production culture is performed by using culture media prepared in the media preparation step. This production culture step is followed by the clarification and chromatography steps. The P&ID of a bioreactor is shown in Figure 4-5.

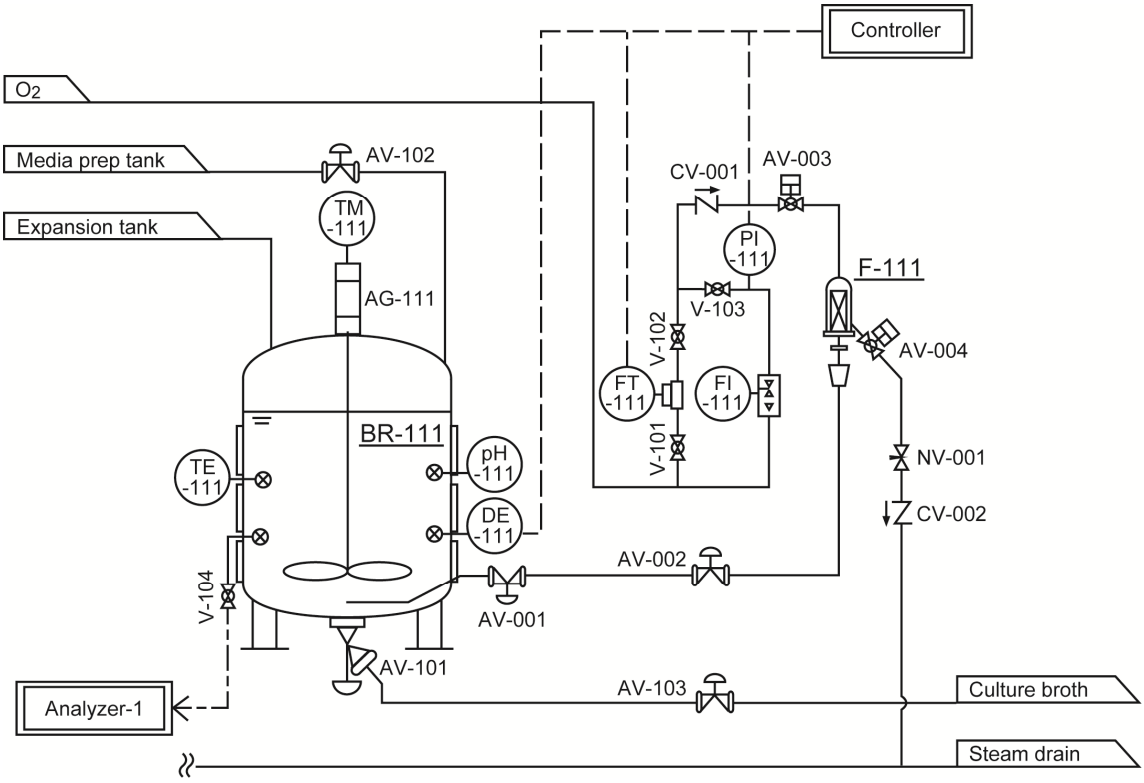


Figure 4-5 P&ID of a bioreactor.

4.3.3.2 Example of Process Deviation Scenario

A simplified process deviation scenario is shown in Figure 4-6. Relationships among deviations are written from the input to output for each process stage. The inheriting attributes of a process stage go to the next stage, but if the output is a failure or deviation over the rejection limit, it no longer continues. Process state failures of controlled states and deviations in performance attribute are shown in the white and black boxes, respectively. Deviations of monitored process states are shown in the gray boxes. A rejection limit failure or deviation is shown in a box filled with a diagonal pattern.

In the prepare media stage, an addition of 20% excess NaCl results in high osmolality (>350 mOsm). If both the mixing rate and time are small, a smaller Vmax (maximum permeability in filtration) caused by insoluble particulates results in an unsatisfied filtrated volume of media. The output of a process stage is written as the input for the next process stage. For example, a media with high osmolality (>350 mOsm) produced in the prepare media stage is input to the execute production culture stage and results in high osmolality (>400 mOsm) of the production culture. The high osmolality and high CO_2 concentration (>25%) caused by a temporal low aeration rate decrease cell concentration (−35% lower than a golden batch), and consequently, the product concentration becomes low (<5 g/L). The

temporal low sparging rate of O_2 gas that occurred in the execute production culture stage results in an increase in the impurity concentration owing to deviations in O_2 concentration, lactate concentration, and final viability. This impurity concentration is consequently related to the output of the execute chromatography stage.

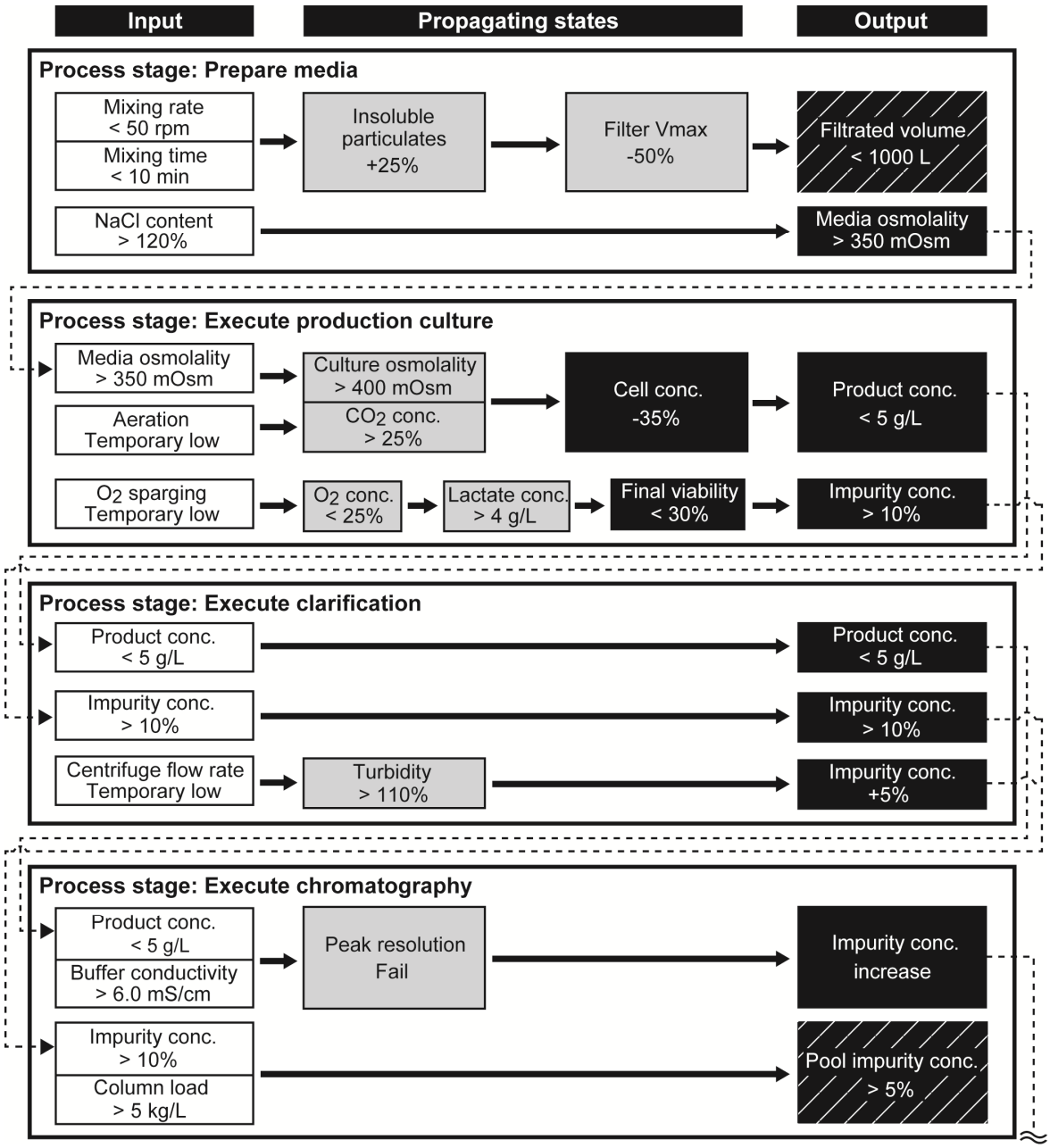


Figure 4-6 Process deviation scenario. White box: a process state failure of a controlled state or a deviation of an adjacent attributes, gray box: a deviation of monitored state, black box: a deviation in performance attribute, a box filled with a diagonal pattern: a rejection limit failure or deviation. The output items which connect to next process stage are inheriting attributes.

This scenario is used to record process chemistry knowledge to enable continuous research and development of quality-based manufacturing processes. In the early phase of process development, the control limits of the process variables are not determined and the cause–effect relationships are only hypothetical. Therefore, a simple scenario is prepared that may not include detailed limits or complex relational information such as the interaction between culture osmolality and cultivation CO_2 concentration. Statistical methodologies such as ANOVA, PCA, and PLS are available to identify out-of-trend process factors. These methodologies support the reasoning of hypothetical relationships in an immature process deviation scenario. They are also available to determine unexpected relationships. The amount of relational information and accuracy of this scenario increases with the progress of process development by applying these methodologies and the solid relational information is recorded as structured knowledge.

4.3.3.3 Example of Procedural Control Scenario

A part of the procedural control scenario written for the execute production culture stage is shown in Figure 4-7. Trigger errors are presented in the white zones. Terminal process state failures of controlled states or deviations in performance attributes are presented in the dark gray zones. The propagating intermediate pathway is presented in the light gray zones. The case of oxygen gas filter blockage is shown as an example triggered by equipment error. The instrument and valve numbers refer to the items shown in the P&ID in Figure 4-5. In this scenario, the F-111 filter is clogged, which decreases the flow of O_2 gas at the AV-002 and AV-001 automatic valves, and consequently, the supply of O_2 gas to the bioreactor decreases. The O_2 gas flow and dissolved oxygen (DO) concentration are detected by the oxygen flowmeter FT-111 and DO concentration probe DE-111 and off-line analyzer-1, respectively. The defense layers against propagation are presented as defense layer-2: O_2 gas flow control and O_2 gas flow alarm (and operator supervision) and defense layer-3: DO concentration alarm and manual interventions (changing filters and opening bypass line). For example, if a defensive function fails, the DO concentration alarm does not work, or if an operator fails to appropriately address an issue, the propagation results in a failure of the DO concentration control. By combining the process deviation scenario and the procedural control scenario, the blockage of the filter F-111 is conducive to an increase in impurity concentration after the chromatography step if the defensive function does not work. Similar

to the DO control example in the execute production culture stage discussed above, scenarios in other stages are also included. For example, an error in opening a control valve between the bioreactor and the centrifuge causes low flow rate in the centrifuge and high pressure upstream of the valve. Sensors to detect these events and possible defense layers to prevent the negative conditions are described.

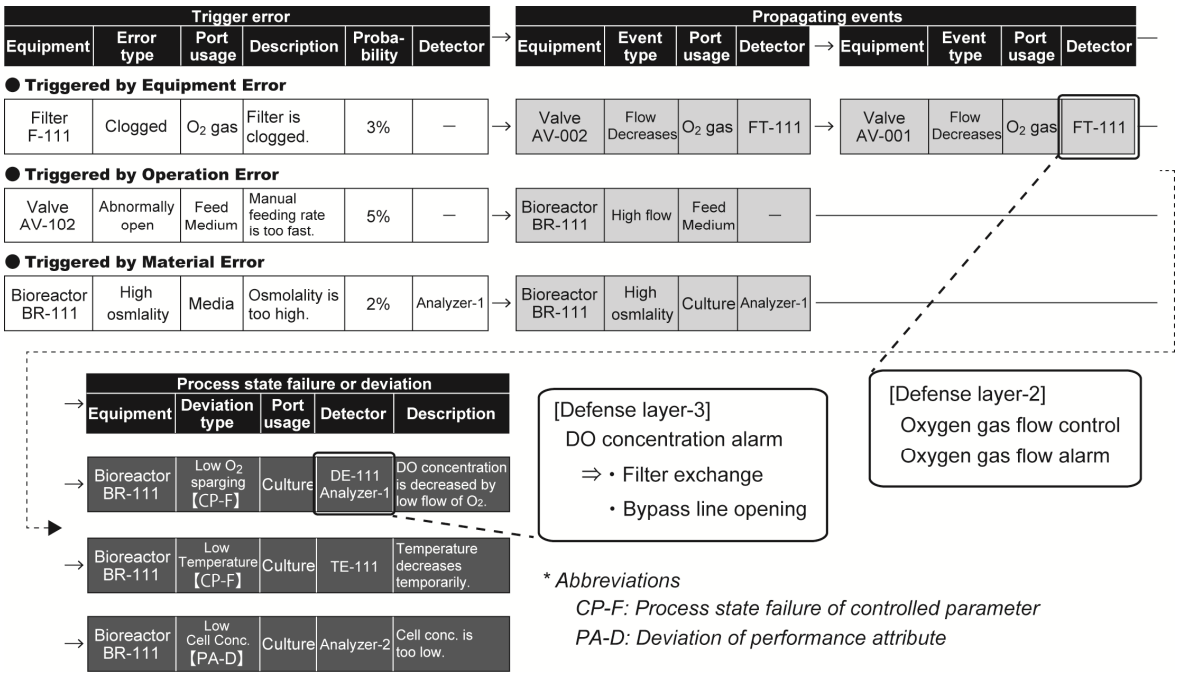


Figure 4-7 Procedural control scenario. White box: trigger error, Dark gray zone: process state failure of a controlled state, Light gray zone: a propagating intermediate pathway.

The case of media with high osmolality is presented as an example triggered by material error. That is, a media with high osmolality is provided as the material for the execute production culture stage. If the defensive function does not work, it is possible that the cell concentration becomes low. In this case, the defense layers involved are defense layer-1: CO_2 concentration is lower than 25%, defense layer-2: culture osmolality alarm and control CO_2 concentration, and defense layer-3: cell growth rate alarm. If these defense layers are functioning properly, protection against propagation is established and deviation is avoided. Defense layer-1 is derived from the process deviation scenario, which shows that a deviation is caused by a combination of deviations or process state failures.

The probability of a trigger error is decided and written in the procedural control scenario. The risk of the occurrence of a deviation can be evaluated by the infinite product of

the probability of all items related to the deviation. Targets to deepen the knowledge of a process and to improve equipment and operation can be screened by this risk evaluation. Other scoring methods for ranking risks (CIA, 1977; Vaidhyanathan, 1996) can be applied to the procedural control scenario if necessary.

4.3.3.4 Application of Quality-HAZOP

An intelligent HAZOP system is already ready for industrial application for process safety, occupational health, and environmental issues (Venkatasubramanian, 2000, Kitajima et al., 2010). Here we focus on constructing a HAZOP system for supporting exchange of risk information. Recipe scientists have knowledge of process chemistry, while plant and process engineers have knowledge of equipment and operations. The Quality-HAZOP system integrates both types of knowledge and facilitates proper control and continuous development of a manufacturing process. Because the system enables determining the equipment and devices related to the control of quality attributes, it supports prompt investigation into a potential risk of a deviation in product-specific processing variables.

If a critical manufacturing error related to a process hazard is detected, possible protection procedures can be determined from among the defense layers in the procedural control scenario. Improvement of the defense layers must be considered if the current defensive function is not reliable enough. When an actual relationship between an error and a deviation is experienced, manufacturing operators and engineers make positive efforts to improve procedures to prevent the propagation. Manufacturing operators and engineers use the Quality-HAZOP for these purposes. For example, the following improvement was achieved by using Quality-HAZOP in a biopharmaceutical process. The process deviation scenario indicated that pH in the chromatography step affects the peak shape of the product's fraction, and accordingly the ratio of charge variants in the product. On the other hand, the procedural control scenario was updated by a HAZOP study conducted by process engineers. The updated scenario indicated that positioning a pH probe on the chromatography skid twisted the cable connected to the probe, thus causing pH measurement fluctuations. Process engineers realized that pH measurement would cause increase of charge variants in the product by using the Quality-HAZOP system and decided to replace the easily twisting cable and improve the procedure for positioning the probe. Since they could recognize the risk to

the process from a quality control perspective, smooth decision making to implement improvements was accomplished.

To achieve lifecycle development of product quality, the risk regarding a specific procedure is analyzed using Quality-HAZOP. The results of the risk analysis propose the improvement of equipment and operation in the order of priority. The process steps for which a large design space should be employed to decrease manufacturing risks are also proposed. When the process deviation scenario is updated through R&D in laboratories or through statistical analysis (such as ANOVA, PCA, and PLS) and continued process verification (FDA, 2011) based on production results, reanalysis of the procedural control scenario is requested (an effect-originated approach). On the other hand, when a new procedural scenario to affect controlled states is found through experiences of incidents and risk analysis such as HAZOP performed by process engineers, the information updates the procedural control scenario and triggers investigations to determine how the process state failures relate to deviations (a cause-originated approach). Even though recipe scientists and process engineers focus only on the process deviation scenario and the procedural control scenario, respectively, Quality-HAZOP can bridge the gap between them. These effect-originated and cause-originated approaches support the continuous development of recipes, equipment, and operations.

4.3.4 Implementation of the Quality-HAZOP

The Quality-HAZOP is implemented as *micks* written in Java on the Eclipse 4.2_Juno workspace. A process deviation scenario on *micks* is shown in Figure 4-8. The overall relationships among process deviations in a production process are recorded and displayed. In the figure, classification and criticality of elements are distinguished by shapes and colors of vertices. The likelihood of a causal relationship between two elements is indicated by the line thickness between two vertices. The lines contain information as to whether or not they are hypothetical. If a relationship is hypothetical, the corresponding line disappears on checking a box. In the early stage of process development, most cause–effect relationships would be hypothetical. Therefore, few items are displayed if the box is checked. Structured relational scenario is developed through visual comprehension as the reasoning of hypothetical relationships is carried out for process characterization studies in laboratory and statistical analysis of accumulated manufacturing data.

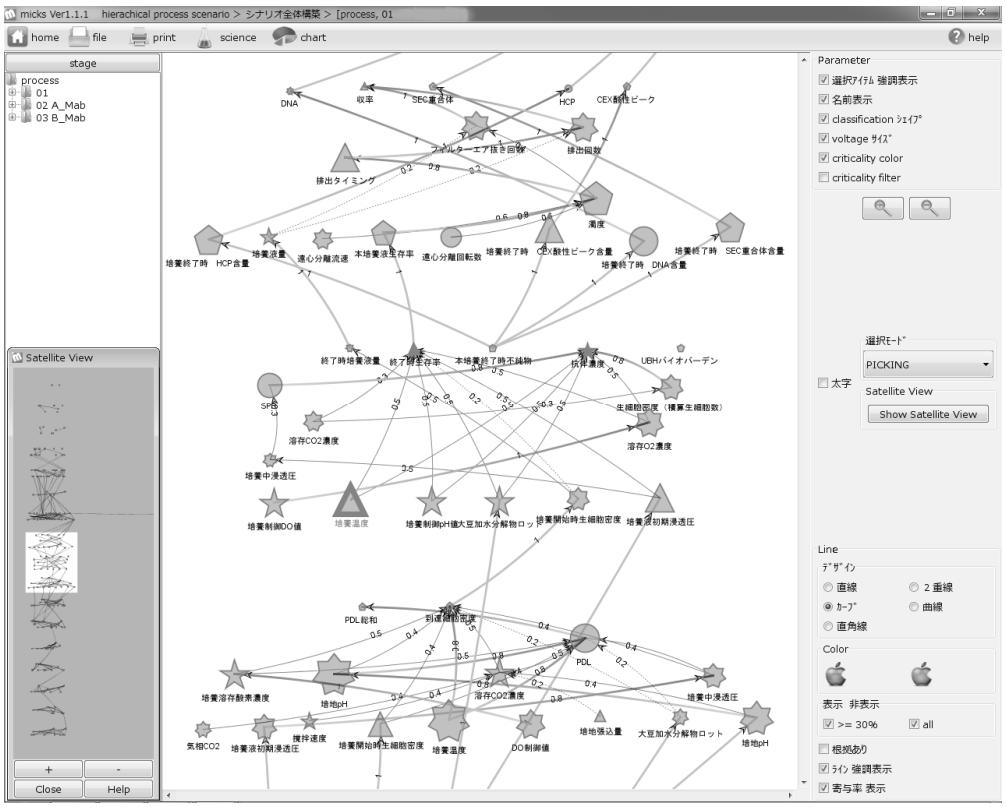


Figure 4-8 Appearance of a process deviation scenario on *micks* (This application is currently written in Japanese).

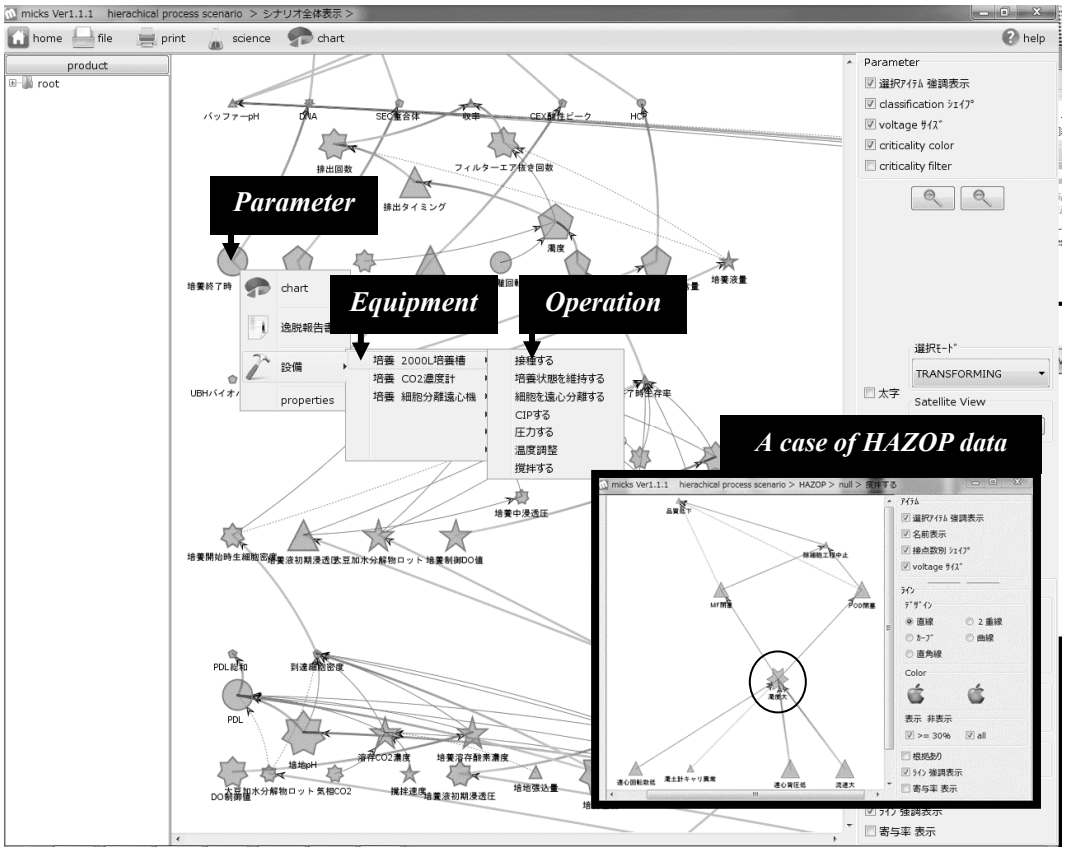


Figure 4-9 Addressing a HAZOP result on *micks* (This application is currently written in Japanese).

HAZOP results are recorded in an operation on equipment. The elements in a process deviation scenario designate related operations. A case of HAZOP results can be searched and found from the process deviation elements via designated equipment and operations (Figure 4-9). This system enables to trace the overall pathway from a procedural error to product quality hazards. Currently, risk assessment using *micks* is limited to qualitative evaluation. Extending the system for quantitative risk evaluation is a future challenge.

4.3.5 Summary

The gap between a recipe scientist's and a process engineer's viewpoints becomes a barrier in the implementation of LCE, because the LCE implementation requires the integration of information on both product-specific processing behaviors and equipment/operation/material-specific processing behaviors. Information on product-specific processing behaviors, which is accumulated by recipe scientists, is summarized in a process deviation scenario, whereas information on equipment/operation/material-specific processing behaviors, which is accumulated by plant and process engineers, is summarized in a procedural control scenario. Personal knowledge is generalized in the two scenarios over the entire lifecycle of the process. The two scenarios are then integrated as Quality-HAZOP by bridging scenarios with the common items in the process state failures. Quality-HAZOP describes the overall pathway from a manufacturing error to product quality hazards. Bidirectional risk information exchange between scientists and engineers is necessary for process LCE. Quality-HAZOP supports the evaluation of overall quality risks among manufacturing processes.

The Quality-HAZOP system focuses on designing recipes, equipment, and operation. Product quality is managed by using more comprehensive information, not only in Quality-HAZOP but also in other chemistry, manufacturing and control (CMC) activities such as change management, incident management, documentation, training, and education. Problem notification or change proposal triggered by the Quality-HAZOP is managed by the activity model-based framework in section 3.3. The information is made widely available by the framework. For example, the problem notification about a twisting pH probe causing pH measurement fluctuations on chromatography skids explained in Section 4.3.3.4 is output from activity A54: Manufacture pharmaceuticals and triggers change management process. All procedures of chromatography in some plants will be improved and the information is

added in a facility design manual. Overall business process management by an activity model system and detailed process development by a Quality-HAZOP system enable implementing LCE requiring the coordination of CMC activities.

4.4 Case-based Reasoning

4.4.1 Introduction

Confidence of relationship between process behaviors written in the process deviation scenario can be ensured by means of statistical analysis of accumulated production data. Meanwhile, development of the procedural control scenario depends on experts' experiences. Case-based reasoning can be applied to find a possible scenario from accumulated cases without experts' support.

In case-based reasoning, problems are solved by using or adapting solutions to old problems (Riesbeck and Schank, 1989). A case is a representation of hidden causal relationship within a process or a problem. Various cases are written in reports that are maintained with the intent of extracting the information that can be used to avoid similar problems while improving product quality. The reports contain data such as deviated parameters, materials and equipment involved in an incident, applied procedures, possible or actual consequences, possible causes, and corrective and preventive actions. Current reports are written in the form of textual natural language descriptions which limit the ability to use past data in an efficient way. Devaney *et al.* (2005) discuss a project for mining maintenance logs using text processing, text clustering and case-based reasoning but no specific results are reported. Anand *et al.* (2006) use association rules for mining a subset of incidents stored in the National Response Center incident database. The association rule extraction is performed by exploring all the combinations resulting from different kinds of equipment and 12 chemicals, which works well for small datasets but requires a computational effort that increases exponentially. This computational effort can be alleviated by formal concept analysis which includes a number of algorithms for a more efficient mining (Estacio-Moreno et al, 2008; Lakhal and Stumme, 2005).

In this section, a case-based reasoning approach which identifies association rules of factors in not only the procedural control scenario but also the process deviation scenario is introduced.

4.4.2 Formal Concept Analysis

The reports are stored in a case base where deviation or incident information follows a predefined structure which includes definitions from domain ontologies. Ontologies define a set of classes (and particular individuals) and a set of relations between these classes for things such as equipment, processing activities, and causality. Ontologies are used to find similarities between parts of the previous cases and the target problem. An ontology describes a shared and common understanding of a domain that can be communicated between people and heterogeneous software tools. An ontology is constructed by defining classes of things, their taxonomy, the possible relations between things and axioms for those relations (Marquardt et al., 2009). A class represents a category of things that share a set of properties. A relation is a function that maps its arguments to a Boolean value of true or false. Examples of relations are *connected_to*, and *part_of*. Class taxonomies are defined with the use of the subclass relation. A class is a subclass of another class if every member of the subclass is also a member of the superclass. ISO 15926 describes classes and relations that can be used to represent things such as processing activities, personnel, plant equipment, chemical processes, batch recipes and engineering diagrams (Batres et al., 2007). The cases recorded ontologically are adapted by means of association rules generated by using formal concept analysis. Similarity between two ontology objects is measured by the distance between classes in regards to their lowest common ancestor. The formal concept analysis has been successfully used in many data analysis and Belen and Pedro (2001) used it for case-based reasoning. It also has been studied in ontological quality management (Poelmans et al., 2013).

4.4.3 Association rules

The identification of association rules refers to the extraction of hidden relations in the logs that permit the discovery of knowledge that includes the identification of patterns in the records, the prediction of the probability that events will occur, and the identification of strong relations between causes and effects. An association rule is a relation between two sets of items A, B that indicates that cases that involve A tend also to involve B.

Identification of association rules is done by processing the data stored in the case base using formal concept analysis. The formal concept analysis is a technique for knowledge processing based on applied lattice and order theory (Wille, 1982). It assumes that data is

represented in as a tuple $K:=\langle O,A,Y\rangle$ where O is a set of objects, A is a set of attributes, and Y is a set of binary relations $Y \subseteq O \times A$ containing all pairs $\langle o,a\rangle \in Y$ such that the object o has the attribute a such as *(Case1, caused by the step spent too long time)*. The initial step in formal concept analysis is to find all pairs $\langle O_i,A_i\rangle$ that satisfy $O_i \subseteq O$, $A_i \subseteq A$, $O' = A_i$, and $A' = O_i$ where A' is the set of attributes common to all objects in O_i, and O' represents the set that has all attributes in A_i. O' and A' are defined as , $O' = \{a \in A | (\forall o \in O_i)\langle o,a\rangle \in Y\}$ and $A' = \{o \in O | (\forall a \in A_i)\langle o,a\rangle \in Y\}$, respectively. Each pair $\langle O_i,A_i\rangle$ is called a formal concept. O' and A' are respectively the *extent* and the *intent* of the formal concept. The hidden relations become apparent by analyzing the so-called concept lattice. A concept lattice is a partially ordered set in which a $\langle O_i,A_i\rangle \subseteq \langle O_j,A_j\rangle$ if and only if $O_i \leq O_j$. Several algorithms for lattice-construction are available. Typically, the set $K:=\langle O,A,Y\rangle$ is represented by a cross table. In this study, O represents the set of cases and A denotes the set of attributes such as specific causes and consequences, equipment categories, product names, raw materials used, products made prior to the event, products made during the event, and impacts to product.

4.4.4 Example

Figure 4-10 shows an assumed illustrative example of cases C1,…,C12 organized as a context table. The cases are reported when carrying out recipes R1 and R2 with errors E1,…,E5 and consequent behaviors B1,…,B3. It is immediately apparent that cases labeled C1, C2, and C3 constitute a formal concept because they share exactly the same attributes {R1, E1, E2, B1} not shared by any other object. Similarly, cases labeled C11 and C12 constitute another formal concept with attributes {R1, E2, B1}. From the lattice it can be seen that {R1, C1, C2, E1}⊆{R1, C2, E1}. There are three cases related to recipe R1 in which E1 and E2 are the cause of B1. From a simple look at these individual cases, three causality alternatives are possible: {R1, E1, B1}, {R1, E2, B1} or {R1, E1, E2, B1}. However, formal concept analysis by taking into account other cases concludes that E1 alone cannot be a cause of B1. Note that {R1, E1, B1} is not included in the lattice, while keeping {R1, E2, B1} and {R1, E1, E2, B1}.

In actual incident data, the context table is not arranged as Figure 4-10. Therefore, it is almost impossible to find a correct relationship from numerous cases. If an unskilled person analyzes the case of Figure 4-10, he or she may easily judge that the both errors E1 and E2

directly relate to behavior B1 from the cases C1, C2, and C3. The case-based reasoning on the basis of the formal concept analysis helps him or her noticing the possibility that the error E2 is direct cause and the error E1 is indirect cause of the behavior B1.

	R1	R2	E1	E2	E3	E4	E5	B1	B2	B3
C1	✓		✓	✓				✓		
C2	✓		✓	✓				✓		
C3	✓		✓	✓				✓		
C4		✓		✓				✓		
C5		✓				✓	✓		✓	
C6		✓				✓	✓		✓	
C7		✓				✓	✓		✓	
C8		✓			✓			✓	✓	
C9	✓	✓					✓			✓
C10	✓	✓					✓			✓
C11	✓			✓				✓		
C12	✓			✓				✓		

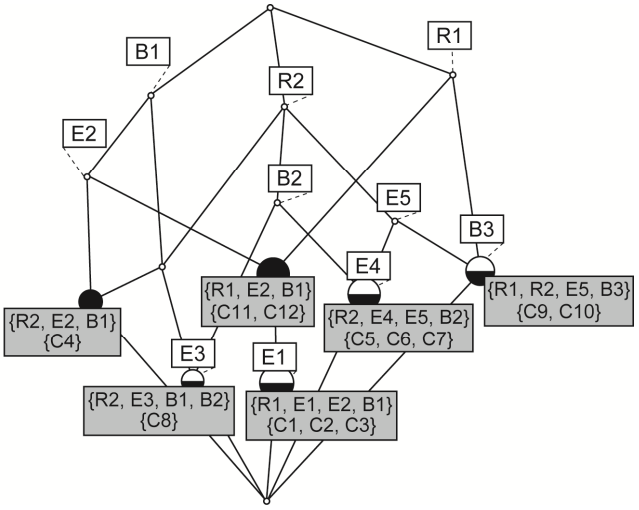


Figure 4-10 A context table and its corresponding concept lattice. C: cases, R: recipes, E: procedural errors, and B: consequent behaviors.

4.4.5 Summary

Case-based reasoning approach based on ontological records and formal concept analysis provides a solution for storing, maintaining, and retrieving information about cases of deviations and incidents. Extracted information can be used to identify what went wrong and what solutions were effective in order to avoid similar cases. The information obtained through the case-based reasoning approach is written in the procedural control scenario of Quality-HAZOP system and triggers investigations to determine how the information relates to deviations.

We applied this approach to 61 incident reports in 2010-2011 of a biopharmaceutical company. The result could indicate no convictive relations, because the applied instances were too discrete, i.e. they included a lot of clearly unrelated cases. Scope limitation is needed to obtain a convictive output. The Quality-HAZOP can be available to find in which part of the process a particular analysis is needed to complement small understandings about relationship between parameters. Preliminary observations indicate that it is possible to identify mutually exclusive classes of events, direct causality, and the relations between events and other entities; however, much work is needed.

4.5 Conclusions

This chapter focused on designing a knowledge-based system for risk information transaction between recipe scientists and process engineers. A structure of such systems for pharmaceutical production process was proposed. Currently available guidelines tend to focus on the definition of process structure from the point of view of recipe design rather than facility design and production. This tendency also appears in the industrial process development and consequently seems to cause a gap between recipe scientists and process engineers. The proposed process structure is intended to classifying process elements for describing relationships not only among process behavioral elements but also among operational elements. Three kinds of new elements, manipulative actions, inheriting attributes, and internal propagating monitored states, were proposed. First, manipulative actions were defined to distinguish operational inputs from controlled behavioral inputs. The definition of this new element helps to clearly describing the procedural control scenario for process engineers. Second, inheriting attributes were defined to connect process stages via their input and output elements. Previously, since output elements and performance indices were confused, the results of a process were not clearly described. Now, the process stages can be clearly connected by using inheriting attributes. On the other hand, performance attributes were defined by testing results of certain states in a process stage to check for satisfactory performance that will lead to process consistency and the intended product quality. Third, the monitored states were defined to describe intermediate causal relationships that occur in process behavior. This classification enables to logically illustrate: (a) the relationships of overall process elements in terms of linkage between process stages, (b) intermediate elements between input and output, and (c) the different views of scientists and engineers.

To bridge the viewpoints of recipe scientists and process engineers, the two scenarios were designed to describe the relationships between product-specific processing behavior and equipment/operation/material-specific processing behavior: the process deviation scenario and the procedural control scenario. The procedural control scenario includes pathways from errors in manipulative actions to process state failures of controlled states. The process deviation scenario includes pathways from process state failures to deviations in monitored states, performance attributes, and consequent product specifications. These two scenarios were then integrated in the Quality-HAZOP bridging scenarios with the common items in the process state failures. The Quality-HAZOP can show the overall pathway from a procedural error to product quality hazards. The process deviation scenario is updated through R&D in

laboratories or through statistical analysis of production results and triggers reanalysis of the procedural control scenario (an effect-originated approach). In contrast, the procedural control scenario is updated through experiences of incidents and risk analysis such as HAZOP performed by process engineers and triggers investigations to determine how the updated risk of process state failures relates to deviations (a cause-originated approach). This bidirectional exchange of risk information between scientists and engineers is necessary for process LCE.

Case-based reasoning was introduced as an effective approach to extract hidden relations in accumulated experiences of incidents while avoiding any prejudice of analyzers. The discovery of knowledge, which includes identification of patterns in the incident records, updates the procedural control scenario. The Quality-HAZOP system can relate discovery to risk of the overall process and can support development of a sound process throughout a product lifecycle.

5 Conclusions and Future Perspective

5.1 Conclusions

This study built a framework to handle knowledge and discoveries obtained in the activities of pharmaceutical process lifecycle engineering. Even though individual engineering methods such as risk assessment tools, process analytical technologies, and chemoinformatics are highly evolved by previous studies, integration of knowledge on a framework necessary to implement pharmaceutical process LCE is lacking. Systematized protocols designed on a framework could manage smooth decision making in LCE. The protocols form a foundation to review and improve current decision making if they are wrong.

Currently an outline of overall pharmaceutical production process LCE abstracting major activities and outcomes can be based on contemplation of a limited number of experts. However, such an approach does not identify where the necessary information for LCE is created and where it should be used. A detailed business process was logically illustrated in an IDEF0 activity model so as to identify mechanisms for information transactions. In pharmaceutical industries, production process LCE is implemented by iterative improvement in the process from early stages rather than in single path development. To manage iterative process improvements, the model clearly defines not only the horizontal PDCA cycle on an activity layer but also the vertical PDCA cycle between activity layers.

This activity model of pharmaceutical process LCE explicitly framed the hierarchical activities of first the Define desired product performance stage, second the Design product stage, and third the three subordinate stages: Design recipe, Design facility, and Produce. This hierarchical structure includes functions of existing decision making processes (administration, coordination, and implementation as shown in Figure 3-4), which are performed implicitly. The protocol to make engineering documents such as the production control chart (Figure 3-4), used in conventional pharmaceutical process development was theoretically redefined on the proposed activity model. By using the redesigned protocol, the

change management process can be supported when any errors appear in LCE. Furthermore, using the proposed model, change management of business rules and/or engineering standards can be managed. Decision making during change management, which is otherwise based on personal memories, are recorded on guide forms that are prepared as engineering standards on the activity model. The guide forms can be continuously improved by accumulating decision making experience and improving defects in past decisions. By designing business process management systems based on an activity model, thorough and bias-free handling of information can be supported. This activity model-based approach could support extensive business processes between projects, development phases, and business organizational structures, and thus could facilitate a holistic and proactive LCE implementation for continuous quality improvement.

Applicability of this approach was demonstrated by case analysis of changes performed in an actual company. After only two minor modifications in the activity model, the model could be applied to 86 cases. This shows that the model is sufficiently applicable to actual changes. This case analysis showed that information was well served to the operation stage, while there was negligence of information transaction from production stage to design recipe and design facility stages. Therefore, the Quality-HAZOP system was proposed to improve information transactions. The structure of a pharmaceutical production process is proposed prior to constructing the Quality-HAZOP. Different views of scientists and engineers were clearly represented. To bridge differences in viewpoints between recipe scientists and process engineers, two scenarios were designed to describe relationships between product-specific processing behaviors and equipment/operation/material-specific processing behaviors: process deviation scenario and the procedural control scenario, respectively. Procedural control scenario includes pathways from errors in manipulative actions to process state failures of controlled states. Process deviation scenario includes pathways from process state failures to deviations in monitored states, performance attributes, and consequent product specifications. These two scenarios were then integrated as the Quality-HAZOP by bridging scenarios with the common items in the process state failures. The Quality-HAZOP can show overall pathways from procedural errors to product quality hazards. Process deviation scenario is updated through R&D in laboratories or through statistical analysis and chemoinformatics on production data and triggers reanalysis of the procedural control scenario (an effect-originated approach). In contrast, procedural control scenario is updated through experiences of incidents, risk analysis by the case-based

reasoning, and HAZOP studies performed by process engineers. Investigations to determine how the updated information relates to quality deviations are then triggered (a cause-originated approach). This bidirectional risk information exchange between scientists and engineers is very helpful for process LCE.

In summary, a framework to handle knowledge and discoveries obtained during the lifecycle of a pharmaceutical production process was designed on the basis of an IDEF0 activity model. It was shown that LCE on the framework promotes more effective use of knowledge and discoveries and that it facilitates PDCA cycle occurring in LCE activities. By using this framework, business processes in pharmaceutical production process LCE can be continuously improved.

5.2 Future Perspective

The framework proposed in this study has started being applied in a pharmaceutical company. A committee composed of 50 scientists and engineers is detailing the activity model developed in this study. The required outcomes, procedures, and guide forms are being developed on the activity model, and some of them are already being used. The committee members express opinion that the activity model-based approach is effective for organizing outcomes that support sound business processes. In addition, attitude of the members seemed to shift through the modeling discussion: at first they were only interested in the handling of information created by other people, but gradually they started to be proactive by giving a thought to strategic information sharing. Interestingly, the challenge to describe the activity model could improve the personnel factors as well as the technical ones in Figure 3-5. However, some negative opinions have also been voiced. Currently, a modeling support tool is not available. The model is just drawn on Microsoft Visio. This software is not user-friendly enough for the members to smoothly design and build IDEF0 activity models. If the prepared outcomes, procedures, and guide forms can be loaded from the model onto a computerized system, activities and task implementation will be more effective. As shown in Section 3.3.6, modifications of activities and model adjustments were applied twice. Reviewing and improving business process may be effectively performed by illustrating the business process in the activity model. But then, the management scheme for remodeling will still be controversial.

The Quality-HAZOP system is still conceptual. Currently, a qualitative evaluation system, which visualizes the process deviation scenario and the procedural control scenario, is implemented in self-programmed application named *micks*. Constructing a system for quantitative risk evaluation is a future challenge. Quantitative evaluation is required to prioritizing targets for further improvement. Some software companies have released systems for acquiring and analyzing data (e.g., Umetrics SIMCA (see: http://www.umetrics.com/ (accessed on September 1st, 2013)) and Accelrys Discoverant (see:http://accelrys.com/products/process-management-and-compliance/accelrys-discoverant/ (accessed on September 1, 2013)). These software packages implement some statistical analysis techniques, such as ANOVA, PCA, PLC, and others. If the Quality-HAZOP system is in accordance with these data analysis systems, knowledge and findings obtained from the data those systems could trigger overall process risk management on the Quality-HAZOP. When the Quality-HAZOP visualizes a process behavioral relationship that is incompletely understood, it could request an analytical target to the analytical software. Such cooperating systems could support a strategic process analytical technology that is based on *what should be monitored* rather than on *what can be monitored*.

In current practice, pharmaceutical companies not only outsource some of the discovery activities but also outsource some of the management of lifecycle engineering and clinical trials to contract research organizations (Lainez *et al.*, 2012; Clark and Newton, 2004; Piachaud, 2002). Since in-licensed products can enter the development pipeline at any stage of clinical trials, the portfolio management decision problem is complicated by both the opportunistic entry and the failure driven exit of candidates over time. In this situation, business process management beyond companies is required. It is almost impossible to manage business process beyond companies depend on personal decision making. Activity model-based management can explicitly specify where the necessary information is created and where it should be used. Combining RACI on the basis of the model, responsibilities between companies can be identified (Sugiyama and Schmidt, 2012 and 2013). The activity model-based management will be more important as functional segmentation progresses.

In Chapter 3, we developed the reference activity model for LCE of biopharmaceuticals, but the modeling approach can easily extend to general pharmaceuticals LCE. The modeling template and relationship of the five activity stages are standard. Activity model-based business process management starts to be discussed in International Society of Pharmaceutical Engineering. The LCE performed in other industries (e.g., food, chemical,

and machine manufacturing industries) could be managed on the basis of a similar framework because the schemes for designing product quality, developing facilities and processes, producing, and maintaining the facilities and processes are the same. We expect that discussions will cover more than any one business category to apply the systems approach in this study to various industries.

Abbreviations

ADCC	Antibody dependent cellular cytotoxicity
ANOVA	Analysis of variance
ANSI/ISA	American National Standards Institute / Instrumentation, System, and Automation Society
BLA	Biologics licensing application
BP	Biopharmaceutical
CCPS	Center for Chemical Process Safety
CMC	Chemistry, manufacturing and control
CPS	Controlled process states
CPV	Continued process verification
CQA	Critical quality attributes
DO	Dissolved oxygen
DP	Drug product
DS	Drug substance
EOPII meeting	End of Phase II meeting
FDA	Food and Drug Administration
GMP	Good manufacturing practice
HAZOP	Hazard and operability study
HCP	Host cell protein
ICH	International Conference on Harmonization
ICOM	Inputs, controls, outputs, and mechanisms
IDEF0	Type-zero method of integrated definition language
IgG	Immunoglobulin G
IND	Investigational new drug application
IPIA	In-process inheriting attributes
ISPE	The International Society for Pharmaceutical Engineering
LCE	Lifecycle engineering
mfg	manufacturing
m-SHEL	Software-Hardware-Environment-Liveware with their management
M, P, E, PR	Manage, Plan, Evaluate, and Provide resources activity
MV	Manipulated variables
NDA	New drug application

MPS	Monitored process states
OHSAS	Occupational Health and Safety Assessment Series
OOS	Out of specification
PAI	Pre-approval inspection
PAT	Process analytical technologies
P&ID	Piping and instrumentation diagram
PC study	Process characterization study
PCA	Principal component analysis
PDCA	Plan, do, check, and act
Pharms	Pharmaceuticals
PIEBASE	Process Industry Executive for achieving Business Advantage using Standard for data Exchange
PLS	Partial least squares regression
PPA	Process performance attributes
PPQ	Process performance qualification
PQCDSM	Productivity, quality, cost, delivery, safety, and motivation (morale)
PQLI	Product Quality Lifecycle Implementation
P.R.	Provide resources activity
PV	Process validation
QbD	Quality by design
QTPP	Quality target product profile
RA	Risk assessment
RACI	Responsible, accountable, consulted, and informed
R&D	Research and development
SOP	Standard operation procedure
4M-4E	Man, Machine, Media, Management, Education, Engineering, Enforcement, and Example

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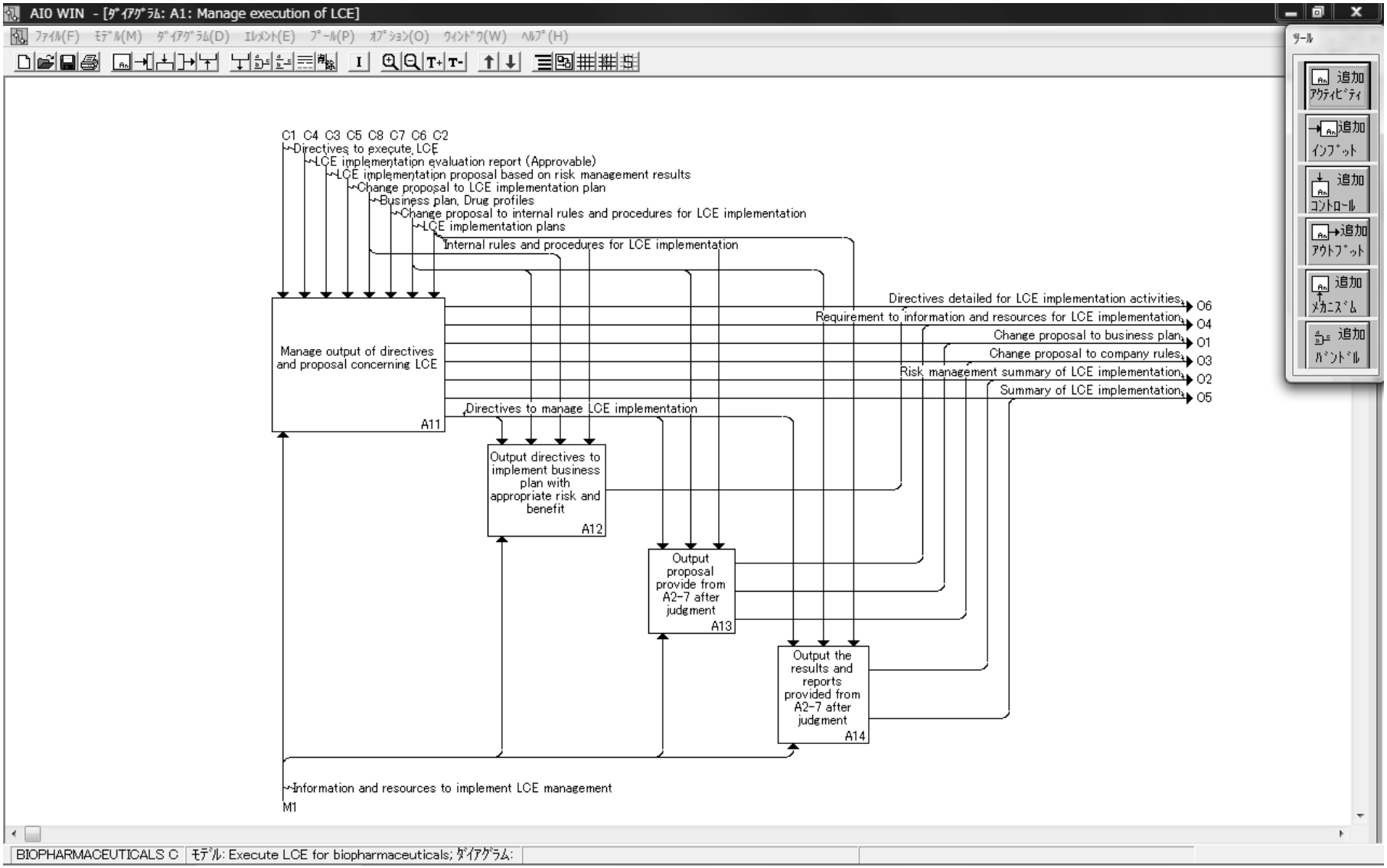
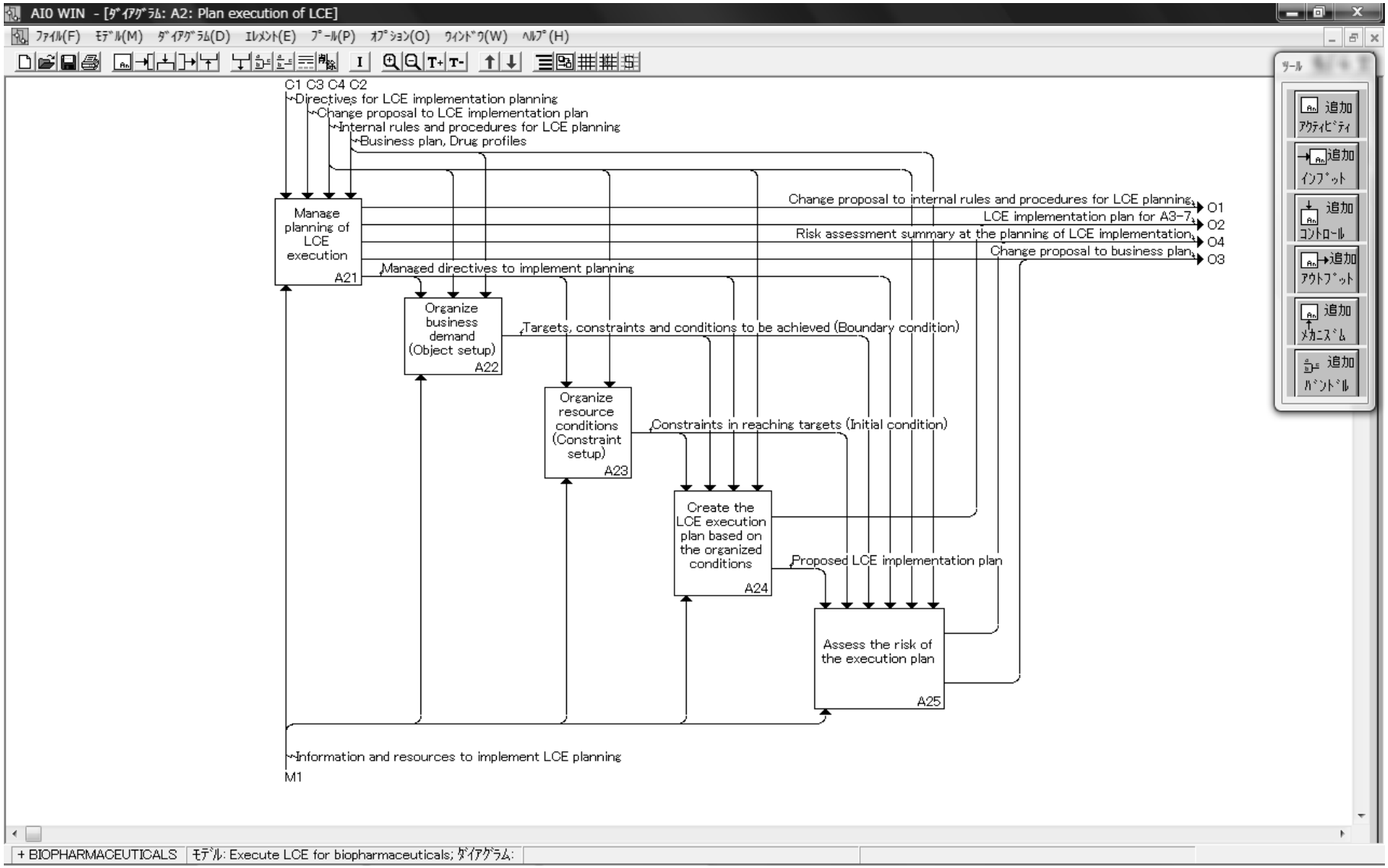
Supporting Information

Appendix - A: Third layers of the pharmaceutical LCE Model

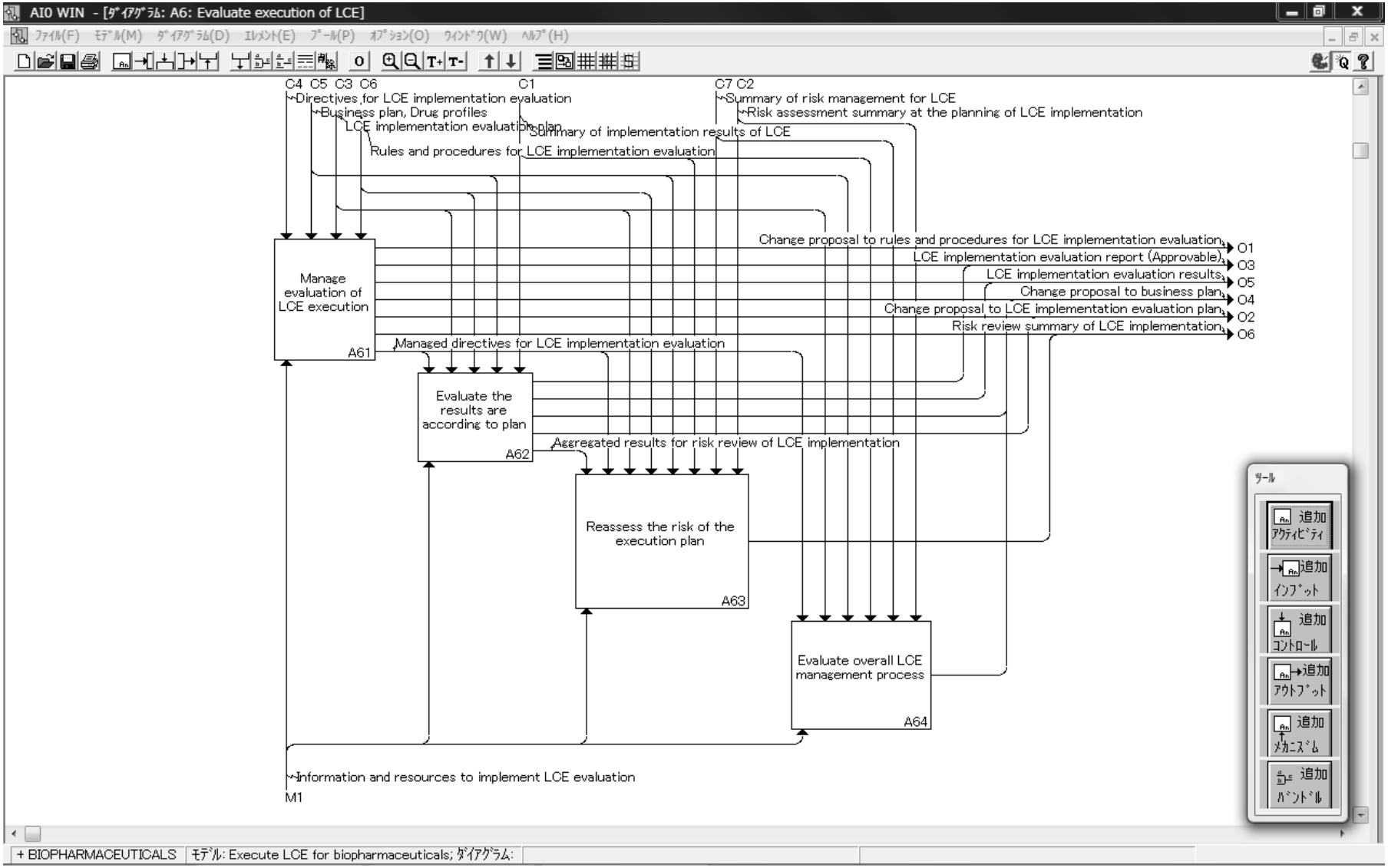
The activities A1, A2, A6, and A7 in third layers of the written model are shown in this appendix. This model was written on AI0WIN Version 8.0, KBSI.



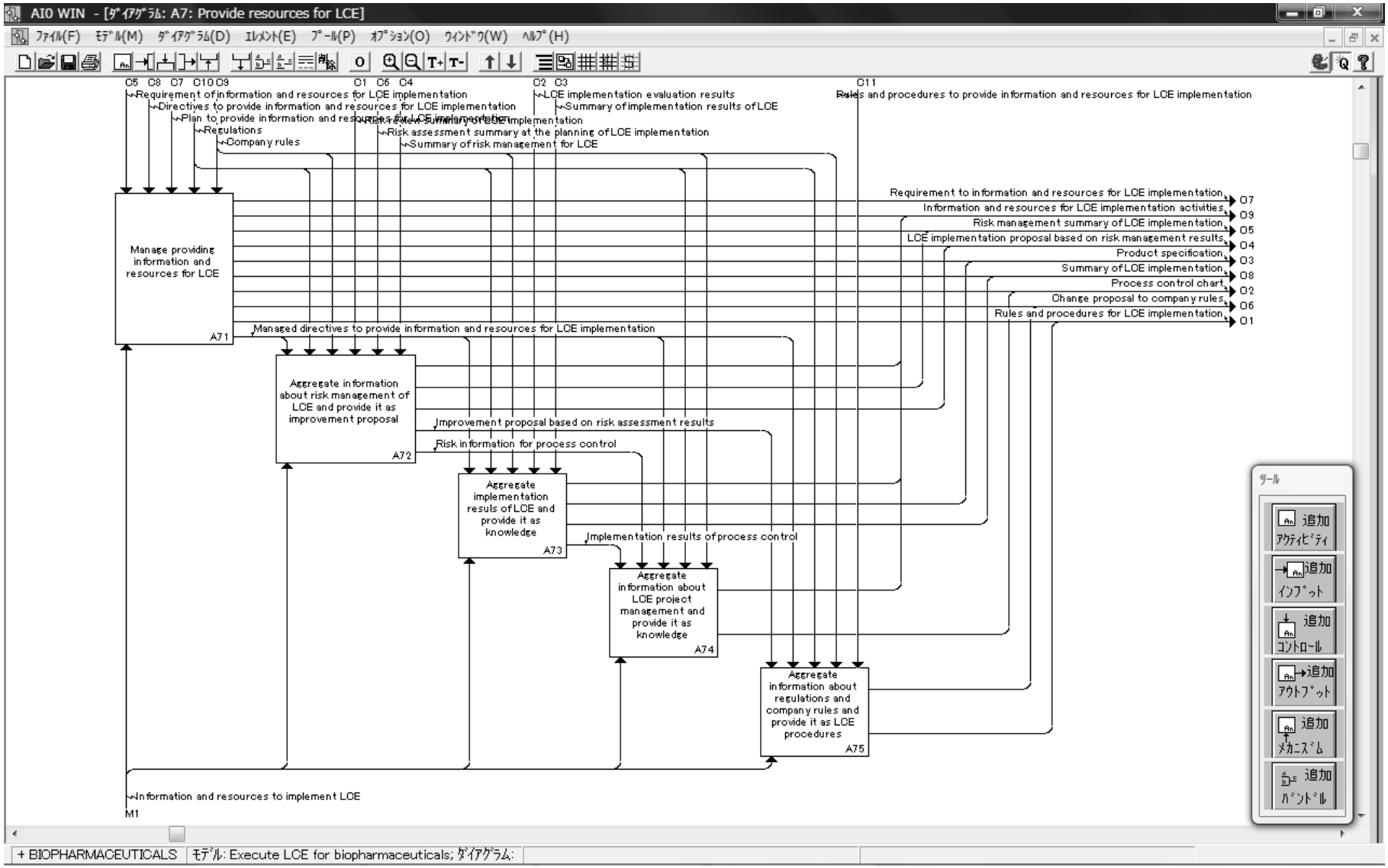
A1: Manage execution of LCE



A2: Plan execution of LCE



A6: Evaluate execution of LCE



A7: Provide resources for LCE

Publication

Original papers

Sugiura J, **Kawai H**, Shimada Y, Tetsuo F, Batres R. (2010) A knowledge-based framework for incident management of pharmaceutical processes, *Computer Aided Chemical Engineering*, 28, 181-186.

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