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
Category(English)	Doctoral Thesis
種別(和文)	論文要旨
Type(English)	Summary

（博士課程）
Doctoral Program

論 文 要 旨

THESIS SUMMARY

専攻： Department of	化学環境学	専攻	申請学位（専攻分野）： Academic Degree Requested	博士 Doctor of	（ 工学 ）
学生氏名： Student's Name	河合 浩史		指導教員（主）： Academic Advisor(main)	関 宏也	
			指導教員（副）： Academic Advisor(sub)	なし	

要旨（英文 800 語程度）
Thesis Summary（approx.800 English Words ）

Intricate modern pharmaceutical business activities strive to achieve lean developments of production processes for desired levels of quality in the lifecycle of processes. Although some guidelines describe the general concept of lifecycle engineering (LCE) and cite individual activities and outcomes, they do not explain overall business process management for product and process development. A guideline, ICH Q10, focuses on business management, but it only covers management responsibility, product and process development flow, and an itemized list of required quality systems. 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 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 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 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. 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. 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. 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.