BPM Support for Regulatory Compliance in ATMP Development Processes

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Abstract

Advanced Therapy Medicinal Product(ATMP) development processes are associated with inefficiencies due to lack of an efficient and effective management methods that can support scientists in working towards regulatory compliance. This research addresses this problem by proposing refined solutions based on knowledge-intensive Business Process Management(BPM). Here, methods will be developed to support scientists in planning a development process that is compliant with regulations. These methods will be based on the knowledge on process modelling, goal modelling and context-aware business processes. Thereby, this project will provide an exemplary approach for supporting compliance management in knowledge intensive processes. The methods will be implemented in a software and evaluated through a real-life ATMP development case.

1. Introduction

Advanced Therapy Medicinal Products (ATMPs) are medicines for human use that offer new opportunities for treatment of many diseases, based on biomedical technology [1]. Development of ATMPs involves several stages and the overall aim in these stages is to develop a safe and effective medicinal product. This is accomplished by collaboration of many stakeholders, where scientists and regulatory consultants are the main ones. Figure 2 in the Appendix describes the main phases and stakeholders in ATMP development.

ATMPs are especially known for their complex regulatory framework. ATMP regulations do not induce strict rules on how things should be done throughout the development. Instead, they involve high-level goals that should be considered in order to demonstrate that the ATMP being developed is safe and effective. There are alternative ways of achieving these goals. Also, regulatory requirements vary depending on the development context. Here, context is defined by the properties of the ATMP. For instance, for different ATMP types (Tissue Engineered Product(TEP), Combined ATMP etc.) or different regulatory classifications of the components of an ATMP (e.g., biomaterial in an ATMP classified as starting material or excipient etc.), different regulatory requirements apply. Also, it is not possible to define the context fully before the development process starts. Instead, different options (e.g., classifying the ATMP as Combined ATMP or TEP) are investigated throughout the development. The flexibility in defining the

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context and variability of regulatory requirements based on context makes it challenging for scientists to manage the regulatory aspects of ATMP development.

Despite its complexity, management of regulatory aspects of ATMP development processes is currently done by scientists in an ad-hoc fashion, which is not efficient. Research shows that, ATMP development processes are associated with many hurdles such as reworks and even withdrawal of the ATMP due to shortcomings in providing adequate evidence of regulatory compliance [2]. This contributes to increased development costs and time-to market. Lack of regulatory knowledge among scientists is an important factor for these hurdles [2]. Being an expert, scientist requires minimal guidance about the scientific aspects of ATMP development processes. However, establishing and maintaining the link between the scientific development process and the regulatory framework of the ATMP development is challenging for the scientists.

Therefore, this project will focus on bridging the gap between scientific and regulatory aspects of the ATMP development to help scientists manage the process more efficiently and effectively.

2. Research Questions, Related Work and Intended Solution

In this project, I propose to support ATMP development processes with Business Process Management (BPM). Traditional BPM focuses on managing predictable and routine work. However, managing unpredictable, flexible KiPs, is an emerging topic within BPM [3]. Considering its characteristics (See Table 1 in the Appendix), ATMP development processes are KiPs. Yet, existing solutions from knowledge intensive BPM do not address our problem, as discussed in the following paragraphs. For applications of BPM to be successful, adapted process management approaches that fits to the characteristics of specific process under consideration is vital [4]. This leads us to the **Main Research Question**.

Main Research Question: How to support preclinical ATMP development processes with BPM in order to help scientists manage regulatory aspects of development process more efficiently and effectively?

The focus of this project is to support scientists in working towards regulatory compliance. For traditional business processes, business process compliance is a well-studied area of research within BPM [5]. There are also significant efforts on compliance management for flexible and KiPs [6, 7, 8]. However, the regulatory requirements for ATMPs have a different nature compared to regulatory requirements for other domains. They are stated as high-level goals, rather than specifying "how" the development process should be performed. Therefore, it is not possible to formalize the ATMP regulations with traditional formalisms, such as the ones in[5]. Moreover, expert interpretation is required for compliance assessment, which makes the assessment flexible. Therefore, a traditional business process compliance management approach is not feasible for this case and a different approach is required. Hence, **RQ-1** is formulated.

RQ-1: How to align scientific development processes with regulatory requirements to help scientists plan the development process?

RQ-1 aims to support scientists in creating a process plan that is in line with the regulatory compliance requirements. To formalize the ATMP regulatory requirements, I will use goal models and to represent development process plan, I will use flexible process models. Here, the

challenge arises from the variability of ATMP regulations. ATMP regulatory requirements vary with respect to the context of development (See Section 1 for the definition of context) and this variability should be represented in the goal models. My intention is to introduce contextual goal models [9] for this purpose. I will also investigate context modelling approaches in BPM [10, 11]. Additionally, applicable regulatory requirements are determined as the context becomes certain throughout the process. So, the requirements are flexible. Therefore, I propose to develop a method that will check the alignment between the scientific development process plan and the goal model of the predefined context and provide recommendations (e.g., prioritization of activities that support multiple goals and/or that should be performed for a wide range of potential future contexts) to make sure the process plan addresses regulatory goals in an efficient and effective way.

In BPM, there exists previous studies to align goal models and process models [12, 13, 14, 15, 16]. Also, the concept of context is not new in BPM [11, 10, 4]. However, our intention here is not only to align the goal and process models or design context-aware processes but also to provide recommendations for better alignment between the process and its goals and creation of an efficient process plan. Additionally, the focus of our method is to support regulatory compliance, which is a different setting compared to model alignment and context-awareness studies in BPM.

Building upon RQ-1, **RQ-2** focuses on providing regulatory compliance support during execution of the scientific development process, formulated as below.

RQ-2: How to provide insights about the achievement of regulatory goals during the scientific development process to support scientists in making decisions about the adjustment of the planned development process?

The method will provide insights about how the results obtained throughout development process contribute to the achievement of regulatory goals. Based on this insight, the expert will be able to make informed decisions about the adjustment of the development plan, e.g. changing the context or redoing process steps. This insight will be provided by reasoning with goal models[17]. Since regulatory goals in ATMP development do not indicate crisp boundaries and values for assessment, the reasoning approach will be enhanced by fuzzy decision making approaches.

In BPM, there are some approaches developed for guiding KiPs in adjustment decisions, that are relevant for RQ-2 [18, 19, 20, 21]. However, these approaches support decisions based on historical knowledge about previous cases. ATMP development is a new field with also a huge variability between different projects. Also, no historical data from previous projects is available for use. Therefore, existing approaches are not suitable for our project. Consequently, input from experts will be used to make the adjustment decisions.

Lastly, **RQ-3** will be answered to evaluate the methods developed.

RQ-3: How can the proposed methods be evaluated?

This PhD project is a part of Horizon2020 iPSpine project[1], in which an ATMP for lower back pain is being developed. The methods will be demonstrated on the iPSpine process management platform, to be developed for iPSpine project, and evaluated by questionnaires with scientists using the platform. Please see Figure 3 in the Appendix for the positioning of research questions.

[1]https://ipspine.eu/

3. Research Methodology

The proposed research methodology, explained on Figure 1, is based on the design science research framework created by Hevner et al.[22].

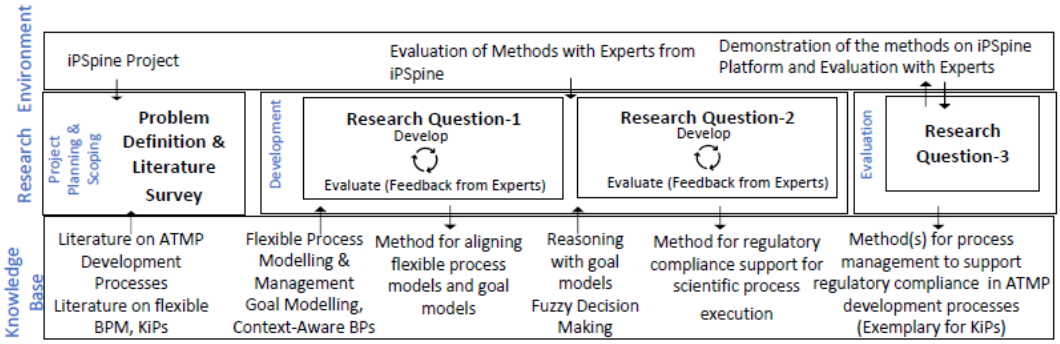

Figure 1: Research Framework

4. Scientific Importance and Relevance to BPM

The PhD project helps to improve the efficiency and effectiveness of ATMP development processes, by developing a BPM-based approach that supports scientists in managing regulatory aspects of ATMP development processes in a structured way. Thereby, from the BPM point of view,this PhD project provide an exemplary approach for supporting compliance management in flexible KiPs with vague and flexible regulatory requirements.

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A. Appendix

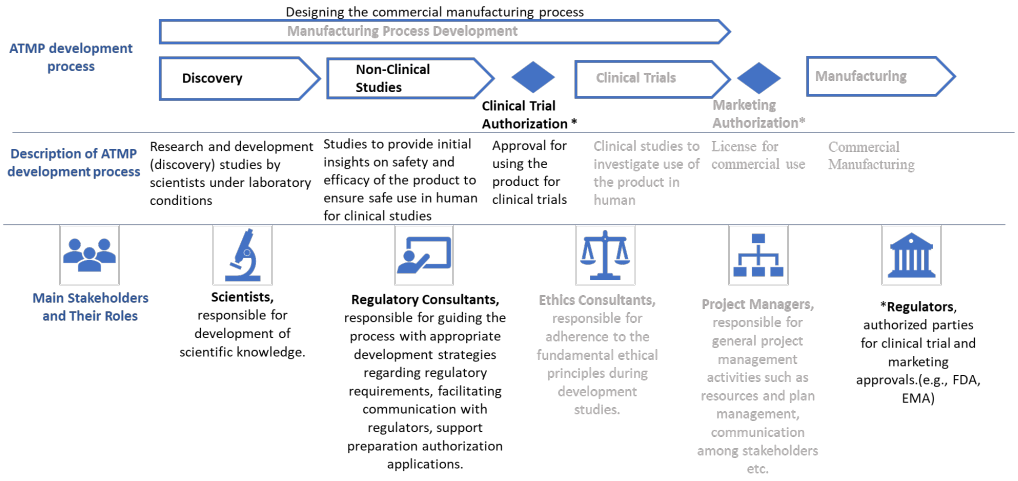

Figure 2: ATMP Development Process & Stakeholders (Stakeholders and Scope of PhD Project in bold)

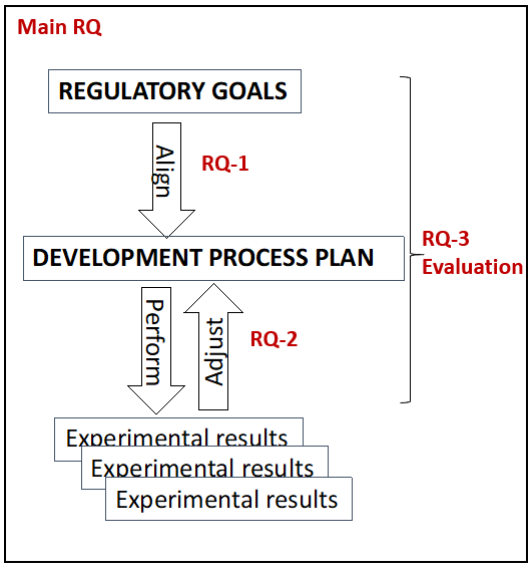

Figure 3: Research Questions

Table 1
Characteristics of KiPs and Relevance for ATMP Development Processes

Characteristics of KiPs	Characteristics Description	ATMP Development Processes
Knowledge-driven	The status and availability of data and knowledge objects drive human decision making and directly influence the flow of process actions and events.	In many cases, emerging knowledge/data together with scientists' interpretation determine flow of process actions.
Unpredictable	The exact activity, event and knowledge flow depends on situation- and context-specific elements that may not be known a priori, may change during process execution, and may vary over different process cases.	ATMP development is an exploratory process. Neither the process nor the knowledge related to the product being developed can be fully prescribed a priori.
Emergent	The actual course of actions gradually emerges during process execution and is determined step by step, when more information is available	It is a search process where realizations throughout the process and availability of certain data/knowledge shape the process step by step.
Constraint- and rule-driven	Process participants may be influenced by or may have to comply with constraints and rules that drive actions performance and decision making.	Compliance regulations and related guidelines should be taken into consideration throughout the process.
Non-repeatable	The process instance undertaken to deal with a specific case or situation is hardly repeatable, i.e., different executions of the process vary from one another.	Development processes are hardly repeatable since in every case, scientific approach, materials used and/or aim of the study and hence related process requirements are different.
Collaboration-oriented	Process creation, management and execution occurs in a collaborative multi-user environment, where human centred and process-related knowledge is co-created, shared and transferred by and among process participants with different roles.	ATMP development process involves many partners with different roles: scientists from different fields, project managers, regulators, companies etc. Each stakeholder contributes to the process.
Goal-oriented	The process evolves through a series of intermediate goals or milestones to be achieved.	Every step (or combination of steps) in the ATMP development aim to achieve a certain goal related to the product being developed e.g. achieving certain levels in safety, efficacy, biomechanical properties of the product etc..
Event Driven	Process progression is affected by the occurrence of different kinds of events that influence knowledge workers' decision making.	Development process is affected by the occurrence of different kinds of events which may be resulting from other scientific or project related actions.