Business Context-Based Approach for Managing the Digitalization of Biopharmaceutical Supply Chain Operational Requirements

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Abstract. The COVID-19 pandemic has brought to attention several supply chain challenges in the globalized biopharmaceutical industry. Demand fluctuations and the ability to effectively repurpose manufacturing facilities, and to dynamically adapt scheduling and capacity to respond to those fluctuations are among the important challenges. The biopharmaceutical industry is highly segmented by geography and competency. Companies often must cooperate with other companies dispersed across the globe. While the manufacturing of final products is concentrated in a few western locations, raw materials may come from other parts of the world and the final products have to be distributed globally. Such a diverse environment is further complicated by stringent regulatory requirements and the lack of standardization for many operational raw materials and customization of product recipes. Therefore, it is crucial to have an effective way to document and use the requirements of different supply chain actors. Still, the requirements are usually written in paper form where one actor specifies a set of rules that other actors must follow to communicate specific information effectively. Digitalization, while promising to address this issue, is a stumbling block because of the complexity of the biopharmaceutical industry. Motivated by this challenge, this paper critically evaluates the novel Business Context-based approach for effective (digitalization) management of supply chain (operational) requirements. Biopharmaceutical supply chain networking is used as a specific case study. The investigation results show that, with identified improvements, the approach has the potential to manage supply chain requirements effectively.

Keyword: Supply chain requirements · Supply Chain · Biopharmaceutical · Business Context

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1 Introduction

The biopharmaceutical market is one of the fastest-growing bioeconomy sectors, projected to reach an 11.3% Compound Annual Growth Rate (CAGR) by 2030 [1]. The market's rapid growth due to ever-expanding treatment options has also led to the globalization of target markets and manufacturing. Namely, companies often outsource parts of their operations and must cooperate with other companies dispersed globally. Consequently, the complexity of the global biopharmaceutical network has led to the need for increased supply chain agility and resilience. Supply chain agility and resilience refer to the ability of a supply chain to quickly respond to changes in supply, demand, and other external disruptions. Yaroson et al. investigated supply chain agility and identified four dimensions of agility - alertness, accessibility, visibility, and willingness [2]. Tukamuhabwa et al. defined supply chain resilience as "the adaptive capability to prepare for and/or respond to disruptions, to make a timely and cost-effective recovery, and therefore progress to a post disruption state of operations – ideally, a better state than prior to the disruption" [3].

Many disruptions in logistics and transportation occurred during the COVID-19 pandemic [4]. These disruptions identified several potential vulnerabilities and optimization opportunities that must be addressed. One of the primary areas of improvement is the digitalization of the biopharma supply chain. Namely, digitalization would permit easier identification and establishment of backup supply routes and help anticipate disruptions in the existing ones. Digitalization of the supply chain is also imperative for one of biopharma's primary development objectives – Biopharma 4.0 [5, 6]. However, the biopharmaceutical industry still needs to achieve this.

To understand why digitalization is a stumbling block for the biopharmaceutical industry, we reviewed previous papers and identified four categories of digitalization challenges. This was important to understand the complexity of the biopharmaceutical industry. One of the challenges is the segmentation of the biopharmaceutical market, so it is crucial to have a mechanism to handle the heterogenous supply chain operational requirements (or capabilities if viewed from inside the organization) of various supply chain actors (e.g., obligatory regulations). The literature identifies two approaches – market mapping [6] and configuration of a supply chain [7–9] – that help analyze such requirements. Still, in practice, these requirements are usually documented in a paper form where one supply chain actor specifies a set of rules, as a free-form text, that other actors must follow to effectively communicate certain information (e.g., Certificate of Analysis).

The contribution of the paper is a preliminary evaluation of the novel Business Context-based approach for effective management of supply chain operational requirements. We use OAGIS Express Pack for Real-Time Release of Raw Materials (RTRRM) [7], recently released by Open Application Group Inc. (OAGi) for evaluation. RTRRM has predefined supply chain messages specialized for application integration in the biopharmaceutical industry. Specifically, we use the Certificate of Analysis message from the package for our evaluation. RTRRM was created by using the Score platform [8, 9], which was developed in cooperation between the National Institute of Standards and Technology (NIST) [10] and OAGi [11].

The remaining parts of the paper are structured as follows. Section 2 introduces the needed background. Section 3 describes the envisioned approach. Section 4 offers a preliminary evaluation of the approach using a biopharmaceutical domain use case. Section 5 discusses the results and future work. Section 6 closes the paper with concluding thoughts.

2 Background

2.1 Supply Chain Requirements

According to [12], "*the biopharmaceuticals market is estimated to be USD 407.72 billion in the current year*". The COVID-19 pandemic significantly impacted the biopharmaceutical industry, and the biopharmaceutical market is expected to grow considerably by the end of 2028 [12]. Acumen Research and Consulting recently published a report that estimates the growth to be at an 11.3% Compound Annual Growth Rate (CAGR) by 2030 [1].

This growing biopharmaceutical market is highly segmented by product type, therapeutic application, and geography [12]. Documenting *supply chain operational requirements* (e.g., obligatory regulations) for each specific actor is essential in such a segmented operating environment. According to Boehlje [13], six dimensions can be used to describe the supply chain requirements: (1) processes; (2) product flow; (3) financial flow; (4) information flow; (5) incentive systems; and (6) governance. Analyzing and documenting these dimensions should assure supply chain sustainability and competitiveness. Zamora defined a *market mapping* mechanism to document supply chain operational requirements that identify and associate all supply chain actors to their environment [14]. The environment defines "the operating conditions within which the actor operates, such as infrastructure, policies, and regulations, as well as institutions and processes that shape the market ecosystem" [14]. Recently, a *supply chain configuration* has been established as an emerging research topic [15–17]. The configuration of a supply chain identifies a set of supply chain requirements that should support operation and information sharing between supply chain actors, across heterogeneous languages, cultures, and regulations. Hernández and Pedersen investigated this topic and concluded that the configuration of a supply chain is complex and requires *constant modifications* to address the changes in specific countries, industries, or companies themselves [15]. The supply chain configuration in the biopharmaceutical industry is further complicated by custom designs, and single sources due to the strict regulatory requirements as well as the inherent "natural variability" typically present in biopharmaceutical production processes. Currently, supply chain requirements are usually documented in a paper or unstructured electronic form where one supply chain actor specifies a set of rules that other actors must follow to effectively communicate certain information (e.g., Certificate of Analysis - CoA). Examples of supply chain requirements are information elements that must be included in the CoA covering acceptance test procedures for specific raw material types (e.g., media, supplements, and buffers), acceptable test results, etc.

Paper-based requirements are difficult to streamline in any subsequent analytical processing, which makes efficient utilization of the contained information challenging. Digitalizing supply chain requirements can streamline existing procedures and facilitate

data-driven decision-making. For example, the reported values for a particular attribute of a raw material that impacts a product Critical Quality Attribute (CQA), or process Key Performance Indicators (KPIs) can be utilized to automatically make production adjustments before raw material utilization within the process. Nevertheless, there are several challenges to digitalization specific to the biopharmaceutical industry. These are discussed in the next section.

2.2 Digitalization Challenges

During the COVID-19 pandemic, many disruptions in logistics and transportation have been experienced [4]. This has hastened the digitalization of the biopharmaceutical supply chains. However, there are obstacles to achieving this. We reviewed the recent literature to identify the most significant digitalization issues and divided them into four categories – complexity, resistance, regulatory compliance, and data integrity.

Complexity. Biopharmaceutical chains are complex [18], segmented [12], and highly globalized [16]. Due to their globalized nature, biopharmaceutical companies must cooperate with small and large partners dispersed across the globe. According to [16], biopharmaceutical companies can be divided into three categories: 1) Biotechnology firms, 2) Traditional pharmaceutical companies, and 3) Generic drug companies. Often, the biopharmaceutical industry requires "just-in-time delivery" because of the limited shelf-life and to ensure timely patient treatment [19] and timely delivery [20]. Moreover, to prevent possible interruptions (e.g., natural disasters, raw material shortage, regulatory changes), many companies practice a "dual-supply" strategy [21]. However, a dual supply chain strategy is difficult because there is a lack of regulatory standardization and, in some cases, highly customized product and production designs. Therefore, they must meet the diverse requirements of scattered manufacturing sites that usually differ in products, technology usage, development process, and obligatory regulations that drive this process [22, 23].

Resistance. Yaroson et al. investigated supply chain agility and identified four dimensions of agility - alertness, accessibility, visibility, and willingness [2]. The supply chain agility depends on its digitalization readiness, and digitalization assumes infrastructural, technological, managerial, and cultural changes. However, the biopharmaceutical industry is still resistant [24] and conservative [2] in accepting these fundamental changes. The main reasons for that are risk reduction [17], finance [25], and information sensitivity [20].

Regulatory Compliance. Grossman and Bates, in their research, stressed that regulatory compliance is a big obstacle for the pharmaceutical industry [26]. To register a new product, a pharmaceutical company must follow product registration procedures and comply with the current compendial requirements defined by local regulatory agencies. Pharmacopeias are used to describe these compendial requirements. Some of the widely-used pharmacopeias are - United States Pharmacopeia–National Formulary (USP-NF) [27], European Pharmacopoeia [28], Japanese Pharmacopoeia [29], British Pharmacopoeia [30], and Chinese Pharmacopoeia [31]. While there are some overlap (for example, British Pharmacopoeia mainly relies on European Pharmacopoeia but has some specific, additional requirements), there are many differences in international standards

[32]. Since many pharmaceutical companies outsource their production processes, compliance becomes an even more significant challenge. Pharmacopeia compliance affects the product throughout its life cycle, from development and testing to commercialization. The acceptance of materials used in a production process and the validity of tests these materials undergo are just some of the variations that pharmaceutical companies need to address [33]. Wiggins and Albanese stressed the need to harmonize and develop global pharmacopeia standards [34]. The World Health Organization's (WHO) initiative to establish Good Pharmacopeial Practices (GPhP) is a step towards this. The last International Meeting of World Pharmacopoeias was held in September 2022 [35].

Data Integrity. The Food and Drug Administration (FDA) agency proposes ALCOA (Attributable, Legible, Contemporaneous, Original, and Accurate) and ALCOA + (Complete, Consistent, Enduring, and Available, in addition) principles that should help govern the data integrity [36]. Data integrity is a big issue that prevents the digitalization of the biopharmaceutical industry [18, 37]. A recent study in 2020 indicated that documents were still stored as hard copies (e.g., contracts), making tracking and validating the procurement process highly demanding and time-consuming [25]. To resolve this, the first step is the digitalization of paper-based systems with electronic ones [38] to assure data transparency, accuracy, and improved information exchange among the supply chain actors [18]. However, several challenges hinder faster digitalization. First, drug serialization, even though mandated by authorities in Europe and the United States, is still an open issue [18]. The second challenge stems from the lack of standards for a specific portion of the process (e.g., eCoAs currently only have one standard, which is not necessarily fully applicable to complex materials). The need for interoperable standards [39] makes integration of systems protracted and, in many cases, business case specific, hindering the adoption of existing standards and incorporation of new standards. This specific issue is essential, considering that the amount of data pharmaceutical companies need to handle is considerably growing [40].

2.3 Business Context

The Core Component Technical Specification (CCTS) is a meta-model standard that enables the development and use of Data Exchange Standards (from here on, standards) [41]. The CCTS uses three critical concepts – Core Components, Business Information Entities, and Business Context. While Core Components represent standard building blocks, Business Information Entities represent profiles of these standard components (i.e., Core Components) restricted for a specific integration use case (e.g., restriction of a value domain, cardinalities, data format, etc.). According to Novakovic, Business Context is "any information that can be used to characterize the situation of an entity within a scope where the business operates. An entity is a person, place, or object that is considered relevant to the execution of a business process in a business environment, including the business process and business environments themselves" [42]. The Business Context is defined by categories describing specific aspects of an integration use case. CCTS proposes eight business context categories, but additional ones can be defined if they are deemed as needed by an integration architect. Recent studies have investigated Business

Context [43], proving it can improve standardization and integration efforts [44]. Moreover, these studies demonstrated that Business Context could be employed to develop the previously mentioned standard component profiles (i.e., Business Information Entities). Three Business Context models are identified in the literature – the UN/CEFACT Context Model (UCM), the Enhanced UN/CEFACT Context Model (E-UCM), and Business Context Ontology (BCOnt) [44]. Each of these models defines a set of operators (e.g., union, intersection) and predicates (e.g., ‘ < ‘(less than), ‘ >’ (more than)) that can be employed to describe more complex integration use cases.

3 Business Context-based Approach for Managing Supply Chain Operational Requirements

Novakovic made a distinction between external and internal contexts [42]. The external context is detected using various physical sensors (e.g., Radio Frequency Identification (RFID), Internet of Things (IoT), Quick Response (QR) code, etc.) that enable traceability of the supply chain. In contrast, the internal context (i.e., Business Context) is detected using logical sensors. This paper focuses on Business Context, as it could lend itself to an approach for managing supply chain requirements. Figure 1 illustrates the proposed approach as a five-step process. Step 1 identifies all factors that regulate the structure and the content of exchanged messages (e.g., COA) in a biopharmaceutical supply chain. Examples of these factors are the geographical location of the biopharmaceutical factory and the target market, pharmacopeias that those markets comply with, raw material type, etc. These factors are to be represented as Business Context categories. Once the Business Context categories are identified, step 2 creates the Business Context knowledge base. According to [44], each category is associated with one or multiple schemas (i.e., sources of values), and the Business Context knowledge base comprises a collection of all possible values for each schema. These steps are crucial as other steps depend on them and must be conducted in cooperation with a domain expert.

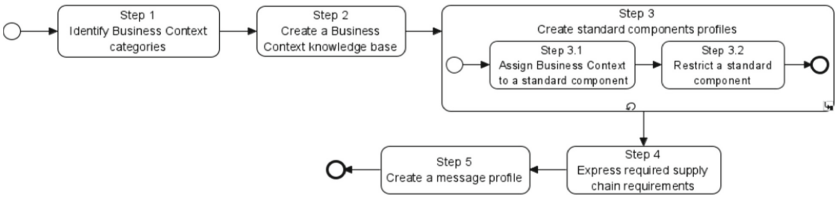

Fig. 1. An approach for supply chain requirements management.

After creating the Business Context knowledge base, step 3 creates standard component profiles. This results in an association of each standard component to a specific Business Context expression and a restriction of that component. Such restriction determines the component's structure and content that are valid for the associated biopharmaceutical integration use cases (e.g., acceptance test procedures, test results, exchange, etc.). Step 3 is repeated for each standard component[1].

[1] The proposed approach assumes a collection of standard components exists.

Step 4 expresses supply chain requirements for the required biopharmaceutical integration use case. The supply chain requirements are defined as a Business Context expression where each category is associated with a specific value selected from the Business Context knowledge base. Finally, step 5, filters the standard component profiles, by using the supply chain requirements, to be embedded in a message profile (e.g., CoA profile). This filtering is based on the *Effective Business Context* calculation proposed in [44]. The Effective Business Context intersects business context expressions assigned in step 3.1 and the supply chain requirements expressed in step 4. Those standard components for which Effective Business Context is calculated as an empty set are treated as nonrelevant and removed for the specific supply chain requirements.

4 Use Case

An OAGIS Express Pack for the Real-Time Release of Raw Materials (RTRRM) developed by Open Application Group Inc. (OAGi) supports digitalization in the biopharmaceutical industry [7]. The Express Pack contains predefined message profiles for the biopharmaceutical industry. The Batch Certificate of Analysis is one of the Express Pack messages; it will be used for the evaluation. Certificates of Analysis (CoA) are fundamental for good manufacturing practice (GMP) and are defined as documents that "provide a summary of testing results on samples of products or materials together with the evaluation for compliance to a stated specification" [45].

Step 1: Identify Business Context Categories. We interviewed a domain expert to identify all critical aspects (i.e., business context categories) that drive the CoA's structure and content. While all message types should be analyzed, we focused on a few CoA aspects, making sure this simplification does not affect the integrity of the evaluation. Four business context categories were chosen after the interviews and analysis of existing documents: Factory Location, Target Market, (product) Purpose of Use, and Pharmacopeia Compliance.

Step 2: Create a Business Context Knowledge Base. Each business context category is associated with an appropriate business context schema that provides a source of business context values for the category. After consulting with domain experts, the classification schema for the Purpose of Use category was defined according to [46, 47], while [48] was used for the Pharmacopeia Compliance category. Figure 2 presents an excerpt of the Business Context knowledge base.

The Business Context knowledge base can be supplemented with logical axioms that bring additional knowledge. Examples of such logical axioms are illustrated in Table 1. A typical axiom pattern is as follows: *A raw material (rm) that* ***complies with*** *European pharmacopeia does* ***not*** *have to* ***comply with*** *British pharmacopeia.*

Step 3: Create Standard Components Profiles. Using a previously created Business Context knowledge base, Business Context can be defined by a combination of values from classification schemas. Each component from the CoA OAGIS Express Pack schema was contextualized using business contexts as shown in Fig. 3. The contextualization assumes the association of a component to a specific Business Context(s). For illustration purposes in this paper, components are prefixed with associated Business

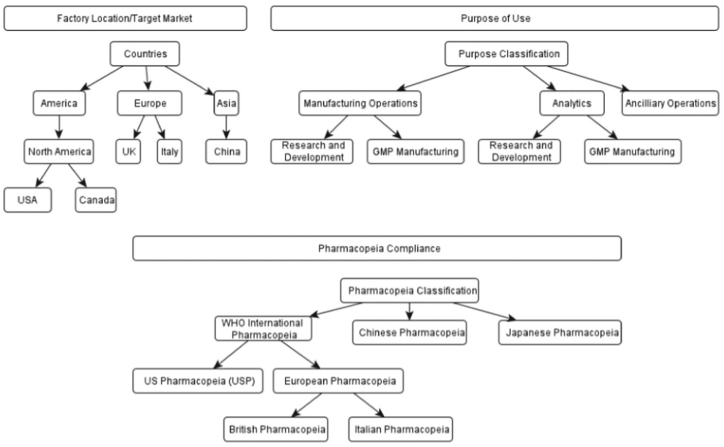

Fig. 2. Business Context knowledge base.

Table 1. Logical axioms.

No	Logical axiom
1	not (compliesWith (rm, European) → compliesWith (rm, British))
2	not (compliesWith (rm, European) → compliesWith (rm, Italian))
3	not (compliesWith (rm, WHO) → compliesWith (rm, European))

Context(s) (e.g., BC_1_Manufacture Date Time, meaning the component is valid only for BC_1).

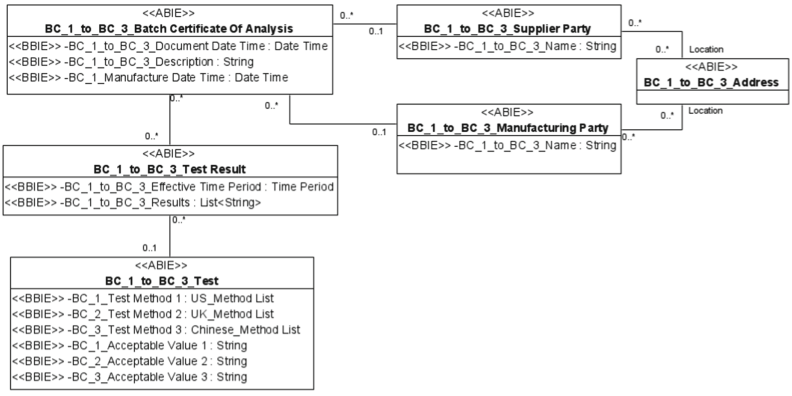

Fig. 3. Business Information Entity – data model.

The definition of each Business Context is provided in Table 2.

Table 2. Business Context.

BC	Factory Location	Target market	Pharmacopeia Compliance	Purpose of Use
BC_1	China	USA	USP	GMP Manufacturing
BC_2	China	UK	British	GMP Manufacturing
BC_3	China	China	Chinese	GMP Manufacturing

Step 4: Express Required Supply Chain Requirements. In the pharmaceutical industry, a CoA is used as a source of information for different raw material information utilization purposes, from sourcing and testing to regulatory filing, where the manufacturer must report compliance with a specific regulatory agency. Because each utilization purpose has particular requirements, the manufacturer needs to adjust the content of the CoA accordingly. Table 3 illustrates three supply chain requirements defined by previously chosen Business Context categories.

Table 3. Supply chain requirements.

Utilization Purpose	Factory Location	Target market	Pharmacopeia Compliance	Purpose of Use
Sourcing & Testing	China	USA & UK	USP & British	GMP Manufacturing
Regulatory filing	China	UK	British	GMP Manufacturing
Regulatory filing	China	USA	USP	GMP Manufacturing

Let us consider a situation illustrated in Table 3 where a manufacturing company located in China wants to put a particular product on the US and UK markets. The product must comply with both the US and UK regulatory requirements for sourcing and testing purposes. The company needs information about all required tests and acceptable values for both markets to ensure compliance. However, for the regulatory filing purpose, where the company needs to report compliance to each specific market (i.e., US or UK), it requires only a subset of the CoA information.

Step 5: Create a Message Profile. Finally, based on the previous steps, creating a specific CoA message profile for each utilization purpose is possible based on the provided supply chain requirements (as defined in Table 3). For that purpose, Effective Business Context is calculated as described in Sect. 3. As a result, three CoA message profiles

are created, as presented in Fig. 4. Each profile contains only information relevant to the corresponding specific supply chain requirements (e.g., requirements for the Regulatory filing purpose). This is important because such profiling permits companies to accelerate and further standardize the exchange of information with suppliers and regulators. Accelerated, standardized, and digitalized communication can ease achieving the raw material Real-Time Release Testing objective. Namely, from the supplier to the manufacturer side, standardized and digitalized communication permits easier access to information on testing results that can lead to decisions such as manufacturing modifications or subsequent in-house testing planning. Also, our approach to standardization and digitalization of communication allows the manufacturer to clearly and easily specify any requirements that the supplier must comply with. Conversely, from the manufacturer to regulatory perspective, standardized and digitalized communication enhances end-to-end data traceability and permits a more streamlined regulatory filing.

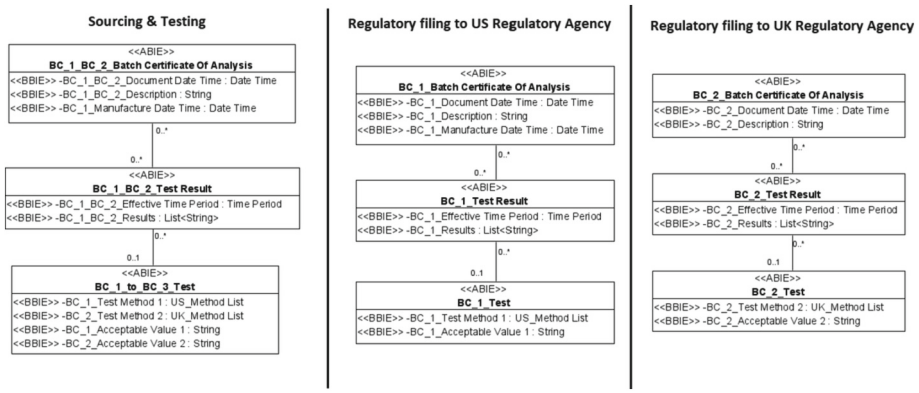

Fig. 4. CoA message profiles.

5 Discussion and Future Work

The use case shown in Sect. 4 has demonstrated that the business context-based approach can be used for managing supply chain operational requirements particularly related the supply chain digitalization. Four categories have been identified as important context categories based primarily on the eCOA requirement driven by the regulatory filing and compliance in raw material. With further analyses of use cases related to the raw material impact on drug products, more context categories such as manufacturing method and product type, will likely be needed. As an example, trace metal concentrations (e.g., manganese) may have different effects depending on the mAb type and could thus have different optimal concentration ranges or testing requirements. Gaining access to this information in a timely manner is crucial for early detection of any out-of-specification conditions as well as, for providing timely insights and data as inputs for adaptive control strategies in the future.

Second, the paper only addresses the supply chain part of the entire value chain. However, there are more types of messages that are fundamental to efficient Biopharma 4.0. Tech transfer where production process information needs to be transferred from the process development to full-scale production is one important area. Future work will focus on inter-company (e.g., to a contract manufacturer) and intra-company tech transfer use cases.

Third, for evaluation purposes, an assumption was made that a collection of standard components is available. The paper used a Certificate of Analysis message from the OAGIS Express Pack for Real-Time Release of Raw Materials. Our previous research efforts have investigated the ability of standards to cover intended integration use cases [49]. The investigation results showed that it is impossible to expect that the standard can cover all variabilities in integration use cases. The main reason is the way standards are developed today. To address this issue, we have been working on a distributed standards development approach that would continuously monitor and collect the requirements of all supply chain actors [44]. Such an approach would ensure that a library of standard components is constantly updated and capable of supporting data exchanges for required variations in a biopharmaceutical domain.

Fourth, in our previous research [49] we have also developed and demonstrated that Business Context can be employed to measure the quality of existing Data Exchange Standard components profiles (see Sect. 2.3). Future work will focus on investigating Business Context as a mechanism to develop similar measures to evaluate the quality of.

6 Concluding Remarks

The paper identified several challenges that delay digitalization in the biopharmaceutical industry and hence the realization of Biopharma 4.0. One of the challenges is the segmentation of the biopharmaceutical market, so it is crucial to have a mechanism to handle the operational requirements of various supply chain actors. In the literature, there are different approaches to analyzing supply chain requirements. However, these requirements are usually documented in papers or free-form text files. As such, the requirements are challenging to streamline any subsequent analytical processing. An envisioned, Business Context-based approach for managing supply chain operational requirements is outlined to address this issue. The approach is evaluated on a supply chain digitalization use case using the electronic Certificate of Analysis from the OAGIS Express Pack for the Real-Time Release of Raw Materials. The evaluation results showed that the approach has the potential to support managing complex supply chain digitalization requirements. To that end, several future work topics have been identified.

Disclaimer and Acknowledgement. Specific commercial systems and applications identified in this paper are not intended to imply recommendation or endorsement by the National Institute of Standards and Technology, nor is it intended to indicate that they are necessarily the best available for the purpose.

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