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A Methodology for Knowledge Management in Biopharmaceutical Production

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This article presents a novel ontological, stepwise approach undertaken to itemize and standardize a biopharmaceutical manufacturing process into a multidisciplinary plant and process knowledge model.

Introduction

Within the biopharmaceutical manufacturing sector, a staggering amount of documented information is required to meet corporate and regulatory requirements. In July 2003, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[1,2,3] introduced an integrated approach to quality risk management. This 2003 workshop agreed on a vision for moving forward with harmonizing finished product GMP to achieve "a harmonized pharmaceutical quality system applicable across the lifecycle of the product emphasising an integrated approach to quality risk management and science."

This agreement led to the establishment of three key topics, or "incremental steps," namely Q8, Pharmaceutical Development,[1] Q9, Quality Risk Management,[2] and Q10, Pharmaceutical Quality Systems.[3] Other key drivers for changes in interpretation of GMP were the FDA's PAT initiative (2002)[4] and the 'cGMPs for the 21st century' initiative,[5] both of which promote a science-based approach to quality systems management and utilizing modern knowledge management techniques. Both ICH Q10 and

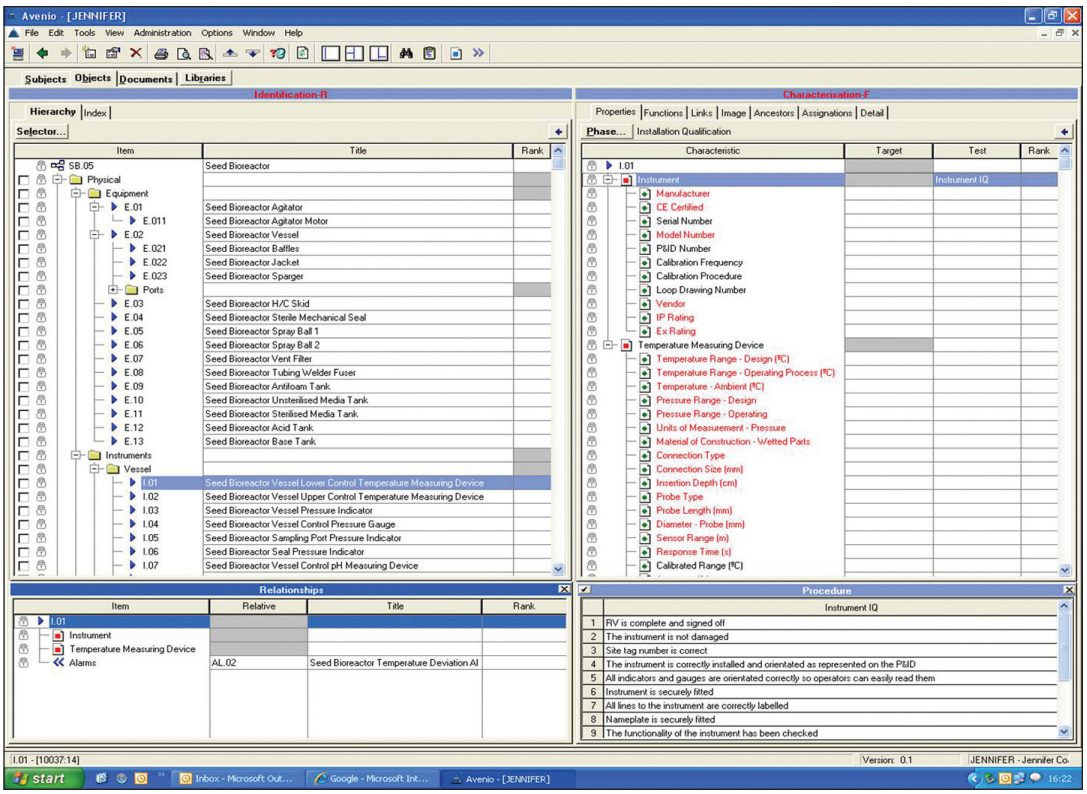

Figure 1. Screenshot of a system, a bioreactor, within the model.

the FDA's PAT initiative specifically highlight the need for centralized databases to capture technical standards, multidisciplinary knowledge, and multi-factorial relationships within a manufacturing environment. One major advantage of such systems would be the potential to standardize plant and process information throughout the biopharmaceutical sector.

The National Institute for Pharmaceutical Technology and Education (NIPTE) in its 2007 strategic roadmap[6] identified "Informatics-Based Model Development and Integration Infrastructure" as a key research requirement to support the pharmaceutical manufacturing sector. *"The lack of formal standards and protocols for representing, sharing, and integrating different types and sources of data and models to facilitate automated decision making,"* was cited as a barrier to the development of these technologies. A research need particularly highlighted was the development of standards and related formal structures, such as ontologies for representing and sharing data and models. In this document, NIPTE also underlined process understanding as one of 10 key areas for research emphasis, indicating the importance of and the need for an increase in fundamental understanding of critical operations and critical process parameters.

While there are many definitions of what is meant by ontology in the fields of philosophy and artificial-intelligence,[7] with respect to the development of a model, which in our case is the biopharmaceutical manufacturing environment, an ontology refers to a formal explicit description of classes. A class can be essentially viewed as a 'type of object' or a 'kind of thing.' The classes within the ontology are described by their properties, i.e., the various features and attributes belonging to the individual class. In creating many instances of these classes, we created the biopharmaceutical knowledge base or model.

The objective of this article is to outline a novel ontological, stepwise approach undertaken to itemize and standardize a biopharmaceutical manufacturing process, into a multidisciplinary plant and process knowledge model. The model developed was structured and inter-connected, yet flexible. The model was primarily used to generate commissioning and qualification documentation across the required lifecycle phases, but also it acts as an easily accessible, centralized repository for knowledge management, such as engineering and quality data, SOPs, electronic user manuals, and P&IDs. All data could be front-loaded into the model, either as individual items or imported in bulk *via* Excel or other spreadsheets/databases. The data was structured and presented as discussed throughout this article and Figure 1 displays a screen shot of a typical system, a bioreactor.

This overall plant model has been successfully deployed on several real life projects and one of the objectives of this research was to demonstrate that a modular approach to plant design is equally applicable on behalf of process. In other words, we wanted to evaluate the models ability to facilitate connectivity between the two layers, particularly in regard to the assignation of criticality, as in "this parameter is measured by this instrument, are they compatible?" We were confident that both challenges would be answered in the affirmative.

Aims

The overall aim of the project was to collate and model detailed plant and process information relevant to biopharmaceutical processing. The initial step in the development of such model was to outline the aims of the biopharmaceutical knowledge model.[8] Firstly, the aim was to provide a common description of the biopharmaceutical production process that could be clearly understood by a variety of users: production, quality, engineering, and technical services personnel. The second step was to determine the overall scope of the model. It was deemed that this model would contain all the essential plant and process information. Common unit operations were broken down into smaller, more specific process steps and plant equipment used within each of these steps, was subsequently modelled in detail.

Thirdly, we aimed to design a reusable database of centralized, multidisciplinary plant and process information to sufficiently model[8] a biopharmaceutical production environment. The final aim was to develop a glossary of terms used within the database.

Methodology

An iterative top-down, bottom-up model and review approach[8] was undertaken using the modelling and validation software, Avenio. The overall hierarchal structure of the model was decided upon initially (top-down method). This consisted of typical unit operations containing the relevant plant systems and process steps, placed in appropriate plant and process folders for clarity. These systems and steps were then filled with the relevant minor components (bottom-up method). The basic procedure for entering a typical item, a unit operation, plant system, or process step was as follows. The software allowed us to select a symbol to represent the desired item, e.g., a bioreactor, which was then identified, using a name or code and a title and displayed on the left hand side of the screen. Each entered item was subsequently characterized in detail on the right hand side and all characterization items were conveniently stored in hierarchical background libraries to allow for single entry, multiple use. Once all the required items, such as plant equipment, instruments, and process parameters had been entered, identified, characterized, connected, and reviewed their respective target values were assigned. These target values could then be compared with the actual attained values for these systems, components, and processes in question to verify their capability to meet the required values. The structure, components, and characterization were then reviewed for suitability and coherency by Subject Matter Experts (SMEs), recommended changes were implemented, and the model was again reviewed (iterative review). Figure 1 displays a screen shot of the database, specifically a bioreactor, with equipment parts and instruments visible on the top left of the screen. The alarms monitoring the relevant critical process parameters for this process step are visible on the bottom left. The detailed information required to characterize a bioreactor is visible on the top right. A procedure for performing an installation qualification on the bioreactor is visible on the bottom right. For the purposes of this research project, only a limited amount of target or actual values were entered into the model, owing to the substantial range of possible assignable values.

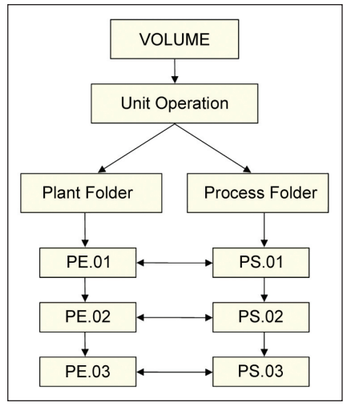

Figure 2. A schematic of the overall hierarchy.

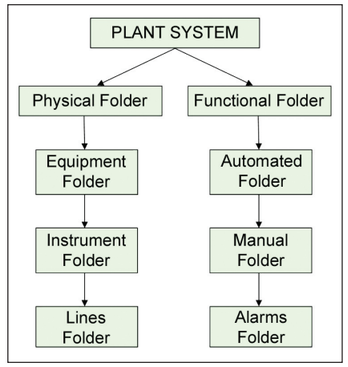

Figure 3. A schematic of the plant system hierarchy.

Naming Conventions

Suitable naming or tagging conventions were established for distinguishing systems and components of the model. These unique names or tags consisted of capitalized alpha-numerics with a period between the alpha and numeric section, e.g., Process Step No. 1 (PS.01). Contextualized titles that were highly descriptive and distinct were given to all items to provide further information; for example, a sampling port on bioreactor would be called: P.01 Seed Bioreactor Sampling Port.

Overall Hierarchy

To begin with, for the process or volume of interest, a generic biopharmaceutical process 'train' was determined. This was accomplished *via* consultation with Subject Matter Experts (SMEs), ISPE and other regulatory guidelines,[9-14] Piping and Instrument Diagrams (P&IDs), and site visits to relevant production facilities.

Ultimately, this process resulted in the development of a process flow diagram. This process flow diagram was then used to sub-divide the process into the relevant unit operations, process steps, and plant systems. Unit operations refer to the basic steps that carry out one function in a multiple operation process. Following this, plant systems, consisting of high level equipment and also equivalent minor process steps were identified and located in the relevant unit operation. For example, the plant system, production bioreactor, and process step (main fermentation) were located in the unit operation (fermentation).

To generate the hierarchy, firstly the numerous, constituent unit operations for the particular biopharmaceutical volume or process were entered into the database. Each unit operation contained a plant and process folder as shown in Figure 2. Each process folder consisted of any number of smaller Process Steps (abbreviated PS), such as PS.01, PS.02, and PS.03. In parallel with each of these process steps, each plant folder contained an equal number of equivalent Plant Equipment systems (abbreviated PE), such as PE.01, PE.02, and PE.03. For example: PE.01 refers to Plant Equipment No. 1 and PS.01 refers to Process Step No. 1.

Plant System Hierarchy

Within each of the individual plant systems, folders were created to provide useful groupings of the various items or components comprising the system.

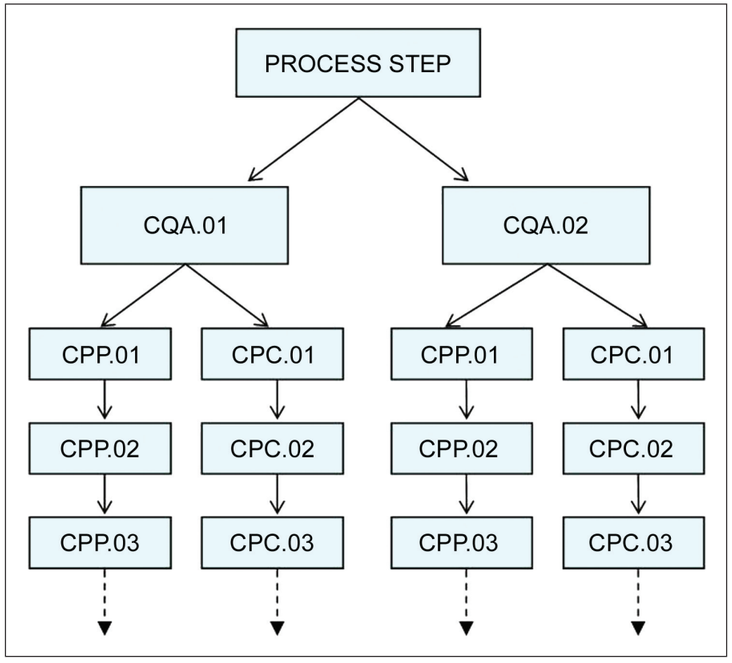

Figure 4. A schematic of the process step hierarchy.

Each system was first split into physical and functional folders, as shown in Figure 3. The physical folder was further divided into equipment, instruments and lines folders, populated with the relevant components, such as equipment parts, attached instruments, and utility lines. The functional folder also was further broken down into three specific types of functions: automated functions, manual functions, and alarms - *Figure 3*. Each of these individual items also could be assigned a criticality level if required; for example, high, medium, or low.

Process Step Hierarchy

The process model was characterized using three types of critical components. The first, Critical Quality Attributes (CQAs), were defined as physical, chemical, or microbiological properties or characteristics that need to be controlled (directly or indirectly) to ensure product quality.[14] For example, biological purity would be a CQA in a filtration step of any typical biotechnology process. Each critical quality attribute was linked to any relevant Critical Process Parameters (CPPs) and Critical Process Controls (CPCs) that could potentially influence it. Critical process parameters are defined as process parameters whose variability impact quality attributes and therefore, need to be controlled to ensure the process produces a product of the desired quality.[14] To take the previous example of an ultra-filtration step, temperature would be considered a critical process parameter, as it may influence the stability or biological structure of the biopharmaceutical product.

For the scope of this project, we have defined critical process controls as critical parameters that cannot be directly measured by an instrument during processing, but can be monitored or tested for before, during, and/or after a process is carried out to ensure the process is/was under control. To provide structure for these components, a subfolder is created to contain the relevant CQAs within each particular process step. For each CQA, the CPPs known to directly impact it, and the CPCs associated with it were identified, as illustrated in Figure 4. Relevant CQAs, CPPs, and critical CPCs were determined for each process step utilizing risk based methods.[2,15] Finally, each CPP was connected via a relationship to the test or procedure used to verify it. These tests could be carried out at any stage of the process, during start up, in-process, or as part of finished product testing and are categorized as such. For example, following a typical biotech process step, such as ultra-filtration, a variety of bioassays would be carried out to check biological purity of the protein.

Classifications

Classifications are the characterization mechanism employed to attach a multitude of information to individual items, such as plant systems, unit operations, instruments, or critical quality attributes.

The information attached using this feature can take a number of forms; for example, instructions, operating procedures, documentation, images, and attributes, as shown in Figure 5.

Items were initially created at 'higher level' (e.g., plant systems and process steps) and subsequently filled with relevant 'lower level' components (i.e., equipment parts and critical process parameters) and characterization could occur at each of these levels. Therefore, each plant system and process step was characterized using a system or step level class. Accordingly, items were characterized at component level, using component level classes. For example, physical and functional components, such as instruments and alarms of plant systems and lower level components of process steps, such as CQAs, CPPs, and CPCs, were characterized at this level. To facilitate the generation of validation documentation, various verification milestones involved in the lifecycle of a typical product were created within the model, such as Design Qualification (DQ), Installation Qualification (IQ), and Operational Qualification (OQ). Using the software platform, it was then possible to 'disable,' i.e., switch off or hide from screen and document view any un-required information attached to items, for each of these various lifecycle phases. For example, during an OQ of a bioreactor vessel, it would be unnecessary to verify the surface finish of the vessel, as this would have been confirmed during DQ; therefore, the attribute, surface finish was disabled for the OQ phase.

All classifications thus created were stored in a central library, therein facilitating a single entry – multiple use

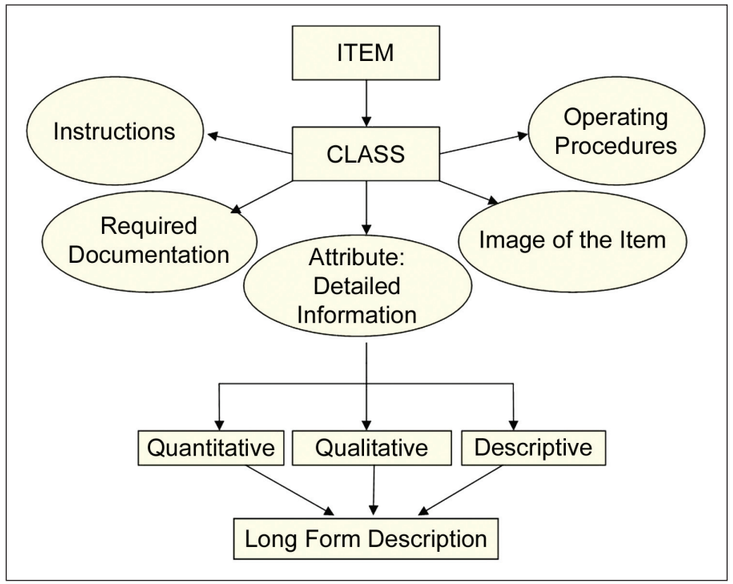

Figure 5. The structure of the classification of items.

concept. This eliminated unnecessary duplication of data and effort. During the population of the database, whenever a plant system, process step, or component was repeated in the model, the original classification stored in the central library could be attached. For example, within the biopharmaceutical process modelled, each time a pressure gauge was required, instead of generating another pressure gauge classification and associated information to be attached to it, the classification stored in the library could be connected. As each classification could be attached to an indefinite amount of relevant items, it was crucial that each classification contained only the essential attributes that provided the information or specifications to adequately detail the component or function in question. For instances of equipment and instrument components, where classifications used often contained large numbers of attributes (i.e., >20), up to two additional classes were attached to the main class. It was determined that each class layer would only contain attributes of a similar level of generality; as a result, classes were created on three tiers: General, Specific, and Detailed. For example, a diaphragm pump was classified and assigned attributes in the following manner:

1. The general class equipment, containing the attributes pertaining to all pieces of equipment; for example, manufacturer, model number, etc.

2. The specific class pump, containing all attributes applicable to pumps; for example, weight and material of construction etc.

3. The detailed class vacuum, containing the relevant attributes to describe vacuum pumps in particular; for example, ultimate vacuum.

Attributes

Of the various types of information that can be attached to the class of an item, attributes warrant specific attention. The attachment of attributes to items *via* their class provided more detailed information (qualitative, quantitative, or descriptive) regarding items.

For example, the class bioreactor, contained the qualitative attribute: Material of Construction, the quantitative attribute: Capacity, and the descriptive attribute: Manufacturer. As required, attributes could be assigned an appropriate target value and continuing on the previous example: the target values for Material of Construction, Capacity, and Manufacturer would be 316L SS, 500, and BioEng Ltd., respectively. Further text, such as descriptive information or prior knowledge, could be attached to each attribute as necessary. The attributes in each general class are inherited by each specific or detailed class. As the attributes of the general class, Equipment, were attached to all manner of equipment regardless of the function, caution was used when determining suitable attributes for this class. It was essential to ensure they were entirely applicable to each equipment sub-class (bioreactor, pump, valve, pressure gauge, etc.). When classifying non-equipment components of the plant system, such as lines, functions (automated, manual, and alarms), and of the process steps (CQAs, CPPs, and CPCs), it was found that one level of classification (general) was sufficient to contain the essential attributes.

For the process steps, all CPPs were assigned the CPP class which contained the attributes Target, Hi Limit, and Lo Limit. Also attached to all CPPs was a risk assessment class, containing relevant risk assessment attributes divided between two folders, Risk Assessment I and II. To perform the risk assessment, we utilized a multidisciplinary group of SMEs, in conjunction with a Failure Modes and Effects Analysis (FMEA) method to evaluate the probability, severity, and detectability of each possible failure mode.[2,15] Risk Assessment I contained the attributes probability and severity, while Risk Assessment II was assigned the attributes detectability and risk priority ranking. The combination of these classes and attributes provided the platform for risk assessment within the model.

Class	Attribute	Target Value
CPP	Target	121.0°C
CPP	Hi Limit	121.1°C
CPP	Lo Limit	120.9°C
Risk Assessment (Folder I)	Probability	Low
Risk Assessment (Folder I)	Severity	High
Risk Assessment (Folder II)	Detectability	High
Risk Assessment (Folder II)	Risk Priority Ranking (RPR)	Medium

Table A. Calculating the risk priority ranking for a variation in sterilization temperature of a vessel outside of the acceptable range.

Table A shows an example of how values assigned to these attributes were used to calculate the risk associated with a variation in sterilization temperature for a vessel outside of the acceptable range.

Connectivity

To provide even greater connectivity between the plant components, functions, and process systems, a series of relationships or 'connections' were created. Within each plant system, instruments were connected to their associated alarms. These alarms were then connected to the CPP that they monitor within the equivalent process step. CPCs were then connected to the particular test used to monitor it. A schematic of the overall hierarchy and connectivity can be seen in Figure 6. As a result of the parallel modelling of the plant systems and process steps, a platform for risk assessment was enabled. Our system could be used to identify CPPs or CPCs in an existing process that are not monitored by instruments or in-process tests that could potentially introduce risk into the process, by comparing it against our model. The screen shot of the database as seen

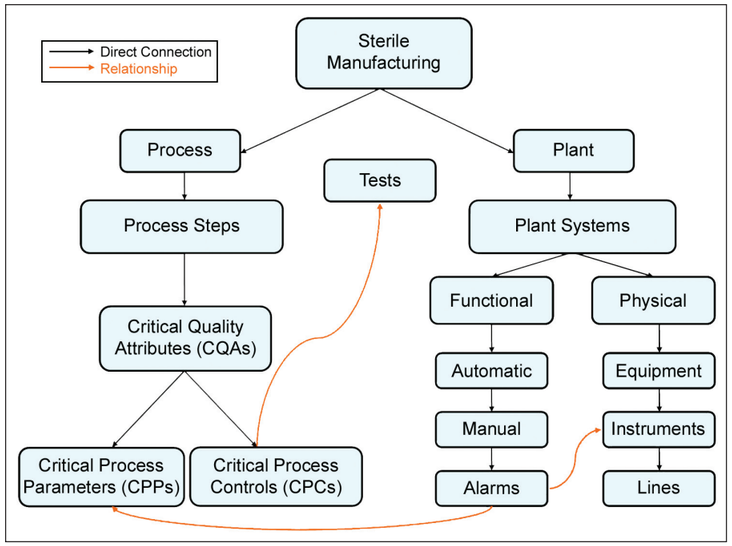

Figure 6. Overall structure of the ontology.

in Figure 1 illustrates a plant system with component parts and attached attributes, relationships, and procedures. The capacity for connectivity between components and their relevant classes, attributes, functions, and procedures is clearly illustrated.

Use

The overall model and software serves as an excellent knowledge management tool and validation documentation generator. With detailed technical and engineering data available immediately, in a concise, useful format, issues such as part or instrument replacement are much simplified and quickly resolved. While the model does not feed from real time, in process information, it can be invaluable in process deviation investigation or Corrective Action and Preventative Action (CAPA). Current approaches to identifying the root cause of a deviation can often be arbitrary and the model assists in streamlining the decision making process. For example, if having sterilized a seed bioreactor, testing revealed the presence of contamination, the model could be used to determine which CQA was affected and provide direction as to which CPP was inadequately controlled and may have led to the unwanted issue. This would result in more efficient and rapid deviation resolution. The software also has several functionalities, which would allow the deviation and resolution to be recorded in a number of formats and attached to the appropriate items at any level.

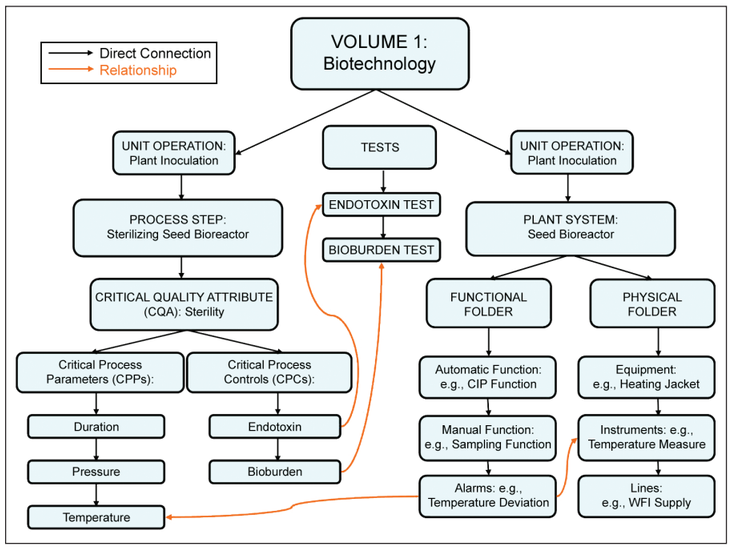

Figure 7. Schematic of a system, the seed bioreactor, and its equivalent process step.

Conclusions

The work performed during this project has resulted in the formation of a novel methodology, which can be used to successfully and explicitly model a variety of biopharmaceutical processes. The methodology illustrates the benefits of structured and reusable multidisciplinary data, information, and knowledge stored in one centralized location. The modelling of the process, in parallel with the plant, allowed for the risk-based determination of the relevant CQAs, CPPs, and CPCs, thereby leading to greater process understanding.

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