



Implementation of a Batch Tool in the Pharmaceutical Industry

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From the beginning of manufacturing operations to the present day, it is possible to notice a huge change. Regardless of the segment, the market has demanded more than the industries have produced, and the trend is that the demand for production will increase in line with the increase in the population and its income. To be able to supply the market and be competitive in their fields of activity, companies rely on the evolution of technology and the implementation of methodologies to be able to increase production.

It is important to consider that the manufacturing processes of one industry are not always valid for another. Because each type of process, be it discrete, continuous or batch, has characteristics intrinsic to its manufacturing method, the methodologies developed for one product will not always be functional for another.

In addition to the concern to serve the market, all industries are studying ways to increase their profit. The first idea to be raised is the increase of production lines or the installation of more equipment. But there is not always the necessary physical space and investments planned to increase the size of the process. So, the question arises: how to increase production without changing the installed base?

In the case of the pharmaceutical segment, concerns go beyond increasing production to serve the market. Because the product contains elements that alter the health status of consumers, the laboratories responsible for manufacturing the products must comply with manufacturing specifications and methodologies established by the regulatory agencies and, if they do not meet these requirements, the product is prevented from being marketed and is taken from pharmacy shelves.

In this article, the characteristics of use and the benefits acquired with a batch process management solution in the

pharmaceutical industry will be shown, as well as compliance with the regulations required by competent bodies with the implementation of the tool.

Types of Process

As previously mentioned, each process has characteristics that differentiate them from each other. According to the manufacturing method, the processes can be of three types: discrete, continuous or batch.

Discrete processes are those that, during the manufacturing process, add independent parts and pieces, resulting in a final product that can be a compressor, a car and even an airplane. Regardless of the complexity and quantity of products manufactured, it is easily classified and listed.

Continuous processes are those in which we notice the occurrence of transformation of raw material into product in a continuous way and through physical-chemical reactions. Generally, the “ingredients” are inserted with their proper concentrations and proportions into an equipment that receives them in operation. An example of this process would be the fractionation tower of a refinery, which always receives oil that results in various products such as kerosene, asphalt, etc. To add the raw material oil, it is not necessary to interrupt the operation of the tower, thus giving continuity of the production process and generating a large-scale product volume.

This type of process has data with strongly temporal characteristics, that is, to identify data in systems developed for these processes, it is enough to indicate the measurement point (tag) and the moment of consultation (time). For this data, trend analysis and correlation between tags generate good results.

Batch processes, in a comprehensive definition, are processes that combine continuous and discrete characteristics. We find this type of process in the most diverse industrial sectors, such as pharmaceutical formulations, food recipes, chemical plants or some paper and cellulose processes. This hybrid feature, combined with the need for flexibility through parameterization, requires special attention when choosing the architecture of the automation and process data analysis system.

Batch processes lead to the production of finite amounts of material, subjecting input materials to a sequence of processing activities over a finite period and using one or more pieces of equipment. These processes have data with continuous characteristics but separated by discrete intervals that aggregate information by item. A typical example is a reactor in a pharmaceutical industry, where we have all process measurements (temperatures, pressures, etc.) stored in time series, related to quality data, such as batch approval, separated by item.

Because it combines the characteristics of continuous and discrete processes, batch processes require specific tools to manage, store and analyze the data of the production process.

Standardization of a Batch System Configuration

To assist in the standardization and communication of batch systems when applied to highly complex processes, in the late 1980s ISA published the first part of a standard called ISA-S88 [Ref. 1] (which was consolidated in the mid-90s), in order to standardize the terminology and modeling of these processes in software tools. These models helped in the development of analytical and administrative tools that easily adapt to these diverse industrial segments.

Segregated in parts that refer to equipment, procedures, process stages, data structure, recipe creation, etc., the first part of the standard (S88.01), defines some types of models. Among them, we can highlight the physical model or physical model, and the procedural model or procedural model.

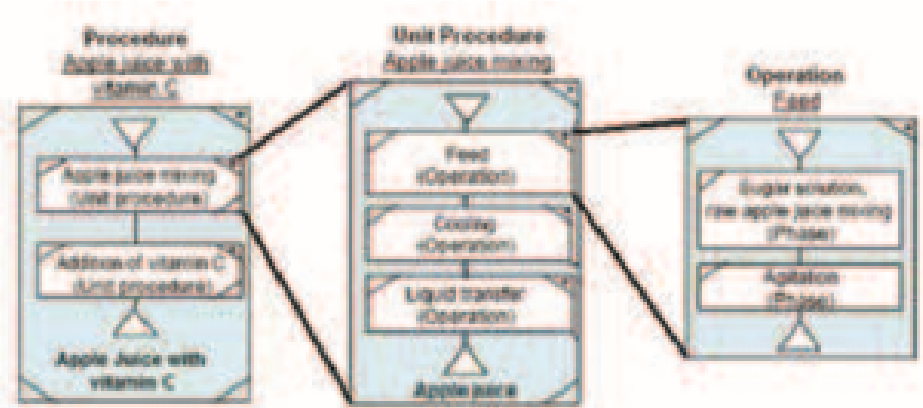
The idea of the physical model is to define the equipment that participates in the production process. There are seven levels that are used to implement the hierarchy of each control equipment within the company.

The scope of action of the ISA-S88 standard within the physical model encompasses only the four most elementary levels, which are: Process Cell, Unit, Equipment Module and Control Module (Process Cell, Unit, Equipment Module and Control Module). These levels are detailed below.

- Process Cell: is the representation of a group of Units that participate in the production of a given product.
- Unit: is the representation of a process unit, such as: tank, reactor, etc.
- Module Equipment Module: represents the control loop. Example: flow control, level, etc.
- Control Module: is the level at which the final control element of the mesh is suitable. Example: valves and actuators.

The procedural model, on the other hand, tries to group the tasks that are performed in the different stages of the process. This model aims to transform a recipe down to the most basic levels of instruction to the controller. Unlike the physical model, four levels are used to define the grouping of tasks, and all are part of the scope of the standard. The levels are: Procedure, Unit Procedure, Operation and Phase (Procedure, Unit Procedure, Operation and Phase).

For a better understanding, the figure below shows an example of the suitability of a process to the Procedural model.



The figure shows, in the first column on the left, the procedure (procedure) of how to make apple juice with vitamin C. The procedure was segregated into two procedures that are performed inside the units (unit procedure): “mixing the apple juice” and “addition of vitamin C.” Within the unit procedure called “mixing apple juice” this general step was divided into three operations (operations): feeding, cooling and transferring the solution. In the “feeding” stage, we arrive at the elementary functions of the process (phases): “sugar and apple juice solution” and “agitation.”

This example clearly shows the purpose of programming within S88: to divide a product's recipe into stages of production until its most basic operation. This way, if there is a need to make the recipe for apple juice without vitamin C, we would not need to program again. It would only be necessary to create a recipe disregarding the “adding vitamin C” procedure.

The transformation of theory into the practice of the S88 concept is accomplished through a programming language called SFC (Sequential Function Chart). The IEC (International Electrotechnical Commission) created the IEC 61131-3 standard many years ago. This is the standard that defines

defines the standard for controller programming. Within them, five programming languages are defined and one of these five is SFC.

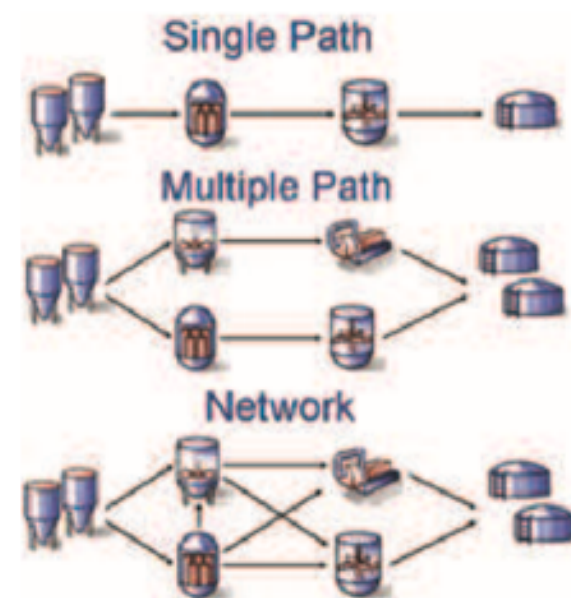
Basically, composed of three elements, the SFC allows to create a graphic sequence of execution of procedures from a typical procedural programming or a more elaborate procedural programming, with the possibility of executing steps in parallel.



The three elements that make up the SFC are: step, link and transition. Based on the figure above, the steps are the gray rectangles. It describes the sequences and operations of the process. Links (connections) are the vertical lines that connect the steps. There is no programming on the links, these are used only to indicate the sequence that the recipe should have. Finally, transitions are used to place a condition in the transition from one step to another, that is, step 2 will be performed only when the condition present in the transition is true.

The S88 standard is more used for batch processes because this process is more complex in the manufacture of the product. In addition to combining characteristics of

continuous and discrete processes, within the process cell (Process Cell) the product can pass through several devices arranged in sequence, which can have a fixed (single path), variable (multi path) or network arrangement (network), as shown in the figure below.



Regardless of the type of equipment arrangement at the plant, they all allow batches to be produced in parallel, whether of the same or different products. To make the most of parallel runs, it is possible to connect the corporate system with the system that manages the dynamic allocation of equipment in the process. Thus, it is possible to scale the production capacity closer to reality and make production planning more efficient.

Pharmaceutical Industry

In general, the pharmaceutical industry has a research and development sector focused on innovation and the creation of new drugs that prevent the spread of epidemics and / or help to improve the quality of life of the population.

The way to reach the formula for a drug that does not exist on the market or that is more effective, is not always simple, nor fast. Most of the research takes years, and there is not always a guarantee that at the end the result will be a drug that can be commercialized. For laboratories, this entire research cycle is treated as an investment sponsored by a percentage of the revenue from products already consolidated on the market. The increase in the production of existing drugs and the optimization of the resources used in their manufacture can generate a profit that can be directed to specific research and, consequently, accelerate the process of obtaining the results.

To monitor the laboratories and establish manufacturing standards that ensure the health of consumers, there are regulatory bodies in each country or continent, responsible for organizing audits in production environments. In Brazil, ANVISA (National Health Surveillance Agency) is responsible for evaluating and monitoring the manufacturing processes of the laboratories. However, if a Brazilian laboratory wants to export its medicine, it must comply with regulations established by agencies in other countries.

In order to facilitate the testing of the necessary functionalities of a manufacturing system, as well as its adherence to industry regulations, a group of pharmacists from ISPE (International Society for Pharmaceutical Engineering) created a methodology with good practices called GAMP (Good Automated Manufacturing Practice) [Ref. 2]. The GAMP provides guides on how to comply with good cleaning practices, good electronic data storage practices, good control systems validation practices, among other guides.

There is a term widely used in the pharmaceutical segment referred to as validation. Validation is nothing more than

proving, through tests, that the implemented configurations satisfy the required needs. Despite the simple definition, validation is a process that is treated with great caution and can take a long time, depending on the size and complexity of the system. All necessary care must be taken with a system that has already been validated, since any change in the configuration that may affect or alter its operation may result in the need to revalidate it.

To ensure the traceability and safety of changes made in the process, there is a rule published by the FDA (Food and Drug Administration) called 21 CFR Part 11 [Ref. 3]. This standard refers to electronic signatures and establishes that all electronic records must be inviolable, and their integrity must be maintained in such a way that it is possible to identify who performed an operation, at what time and what was the alteration practiced.

Gathering all this important information and standards that must be applied in the Brazilian market, ANVISA together with members of ISPE Brasil, created the document called the Computerized Systems Validation Guide [Ref. 4].

Implementation of a Batch System in the Laboratory Aché

Aché Laboratórios Farmacêuticos S.A. is a 100% national capital company. Along its trajectory of more than four decades, Aché has consolidated itself as a dynamic company by establishing strategic commercial partnerships, inside and outside the country, for its expertise in similar medicines, management of a mature portfolio, knowledge of the Brazilian consumer market, and for the continuous development of products and services, in order to meet the needs of health professionals and consumers, providing health and well-being to the population.

With around 3.5 thousand employees, it has three industrial plants. The largest of them, located in the municipality of Guarulhos, in Greater São Paulo, also houses its administrative headquarters. The second is installed on Avenida Nações Unidas, south of the city of São Paulo, and the third in Goiás, with the acquisition of 50% of the pharmaceutical company Melcon, specialized in the production of female hormones.

In its strategic direction, to operate as a complete solution company, Aché operates in the three key segments of the pharmaceutical sector: Prescription, Generics and Non-Prescription Drugs (MIP). It maintains a broad portfolio, with more than 250 brands marketed in approximately 600 presentations.

Scenario Prior to the Implementation of the System

Within the liquid unit of the Guarulhos plant, there were numerous products to be manufactured and a great variability in production times. All steps specified in the prescription of a drug were performed manually. With great difficulty in stipulating a production delivery time for a given batch, previous batches were analyzed, and a difference in execution times was found between the handlers responsible for producing batches of the same product.

In order to standardize the operating times until reaching the final product, a study was developed to verify the need to implement a tool capable of automatically managing the batch production process.

After this analysis, it was found that with the reduction of manual interventions in the process, it would be possible to achieve a forecast closer to reality regarding the delivery time of a batch.

With an implementation date scheduled, the automation system of the liquid unit had the challenge of creating a standardized platform, based on international software development standards and in compliance with the main regulatory agencies of the pharmaceutical sector in the world.

To overcome the challenge, it was necessary to obtain a software platform that was built under the norms of the pharmaceutical sector, facilitating the adaptation of the production process and the personnel involved in the production of medicines to the new system.

In addition, the characteristic of being built under industry standards would facilitate the process of validation and qualification of the new computerized system.

Solution Adopted

With the choice of the Proficy product line from GE Digital, through its distributor Aquarius Software and implementation by Link Automação, all the resources available in the S88.0 construction standards, have earned their reputation and, with the property of building libraries, the classes, phases and operations of the system, it was possible to implement a complex project, in a very short period of time and with great quality, eliminating the risk of building errors.

The first step in implementing the system had already been taken successfully, but the software platform needed to be documented according to the requirements of good manufacturing and documentation practices GAMP and FDA 21CFR part 11.

As the platform was built under the guidelines of the pharmaceutical market, the software adapted perfectly to the resources requested by GAMP and 21CFR Part 11, making

the documentation, testing and correction system a process capable of being accurately measured and with perfect adherence to regulations.

As the validation and qualification process in the pharmaceutical industry is rigorous and delicate, all settings must be documented with excellence in all stages. At this stage of the project, if the software platform is not fully compatible with the norms and good practices of the sector, construction errors or problems of adaptation of the new system to the production environment will be found, condemning the computerized system to failure.

With the second step successfully completed, it was necessary to create the recipe models (Procedures) that would be used in the new computerized system and plan the installation of the system.

The creation of the solution based on the S88 standard allowed the system to use all the physical resources installed in the production unit, transferring these resources to the drug production recipes.

At the same time as the recipes were created, another work team performed the tests of the recipes already implemented, validating the entire system in an almost parallel work format. The programming and connectivity resources with databases and objects provided by the software platform were fundamental for the success of the recipes to be achieved. In addition, the native Client / Server features and the ability to fully adapt to the operating system and the distributed architecture, with different levels of security, allowed the implementation to be carried out with several work teams at different levels of the system. With electronic work messaging resources, the construction of product recipes reached the highest quality standard and, at the same time, the operator's proximity to the system, facilitating the development and acceptance of the solution by the operation team.

In this stage of the project, the construction, documentation, testing and implementation steps had been successfully completed and the system needed to guarantee the return on investment and provide resources to optimize the process, through the analysis of the implemented revenue structure.

In order to resolve this issue, total compatibility with the S88 standard was essential, because through a detailed study of the recipe structure, it was possible to decrease the number of steps, reducing the software cycles and automatically shortening the production time for each product.

The recipes were created using the SFC (Sequential Function Chart) language, which facilitates the organization because it graphically describes the sequential execution behavior, facilitating the visualization of the actions that will be performed and the transition conditions that will be necessary for the next step to be initiated.

The availability of the system was guaranteed with a solid hardware and software redundancy structure, which offers the necessary security for the production process. With redundant database servers and supervisory systems, several process data recording locations, the system continues to operate even if many hardware items fail at the same time.

Currently, the data generated by the management system is stored and traceability reports are consulted by the supervisors of the production unit and quality assurance department, to monitor the quality of the production.

Benefits with the Implementation of the Management Tool

With the implementation of this system, which is easy to operate, where it is possible to monitor in real time all the resources that are being used and the products that are being manufactured, there was a significant increase in production capacity.

The use of electronic signature in all interventions carried out in the process with configuration of hierarchical levels ensures the registration of events and system actions, avoiding interventions by unauthorized people and ensuring that operations are being carried out consciously, with the user's confirmation and password. A typical example is the release of recipes for production that are carried out only by the Quality Assurance area.

With the reduction of human interventions, it is possible to define the start and end times of production much more effectively, considering the product and the lot size, guaranteeing precious information for an efficient and dynamic management of the production process. In addition, the possibility of human error has decreased, ensuring standardization and execution of all steps in the same sequence and time interval.

Due to the system being based on the ISA-S88 standard, its maintenance is easy to understand, saving time and technical resources, and ensuring a longer time of availability for production.

Bibliographic References

[1] ISA S88 – <http://www.wbf.org/>.

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Source: <http://www.aquarius.com.br/wp-content/uploads/2018/05/InTech143-Batch.pdf>

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