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LCA Tool for Sustainability Evaluations in the Pharmaceutical Industry

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This article describes an Excel based tool specifically designed to perform the life cycle assessment (LCA) and the sustainability evaluation of pharmaceutical products and /or processes. In the current state of development the tool deals with the case study of the production of a lyophilized product for intravenous injection, with an active pharmaceutical ingredient (API) produced by fermentation using genetically modified organisms. A gate-to-gate (GTG) analysis is done, considering the API production, the final product formulation, its storage and distribution, and the auxiliary operations involved. These steps are included in the aforementioned tool, and a set of sustainability indicators is proposed to make a quantitative sustainability assessment of this pharmaceutical product and process, based on the relevant impacts identified on its life cycle. Despite the limitations, the LCA and the sustainability assessment tool presented here can be easily modified to other types of pharmaceutical processes, given that good descriptions of them are available.

1. Introduction

Over the last years, the awareness of the importance of sustainability as a key issue for every company's performance has grown considerably. Companies are increasingly being asked to perform their activities in the most environmental friendly way, not only with regard to internal processes but also in relation to their customers and suppliers, throughout their value chain. Although no standard methods are available to guide companies in the integration, measurement or even communication of sustainability (Geibler et al., 2006), the evaluation of industrial processes is normally based on metrics or indicators, depending on the company environmental and sustainability goals (Veleva et al, 2003). The identification and selection of the most relevant sustainability indicators to use should be based on life cycle thinking or supply chain analysis (Mata et al., 2003, 2005, 2011; Smith, 2010). In this regard, LCA has become one of the most relevant methodologies to help organizations accomplish these goals. It can be used to perform a systematic and quantitative evaluation of the potential environmental impacts (PEI) of a product, service, or activity across all its life cycle stages (Morais et al., 2010, Mata and Costa, 2001), and is fully described by the ISO 14040 (2006) standard.
Concerning pharmaceutical products or processes, very few LCA studies can be found in the literature. Among other reasons, this may be due to the difficulties in measuring the inputs and outputs data, lack of information and/or methodologies to evaluate the environmental impacts of some of the chemical compounds used, or the need for protecting the intellectual property created and other sensitive

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information used in the research and development of a new API, which limits the access to or release of relevant information. Also, the available LCA software, including databases, contains scant information of relevance to pharmaceutical processes. Additionally, these tools are too much time consuming and complex to use, not user friendly, and generally do not address concerns of social sustainability or the process economics. The few studies available for biotechnological processes suggest that the most effective way for increasing the process environmental performance is by optimizing material and energy efficiency (Jiménez-Gonzales et al., 2004; Kim et al., 2009; Ponder and Overcash, 2010; Wernet et al., 2010). Other studies conclude that it is the API production that determines the most of the ecological consequences for the activities down the supply chain (Jong, 2003).
The main goal of this article is to present and describe an Excel based LCA tool specifically designed to pharmaceutical processes, and to propose a set of indicators adequate to assess their sustainability. For its development it was considered as a case study the GTG analysis of the production of a biopharmaceutical lyophilized drug for intravenous injection. The API is produced by fermentation using genetically modified yeast. The tool was designed in such a way that other pharmaceutical or chemical processes or other life cycle stages can be easily incorporated in future.

2. Pharmaceutical process description

Pharmaceutical processes are generally divided in two main processing stages: primary and secondary. The first is related to the API production and the second to the final drug formulation that includes the API.

2.1 Primary processing

The primary processing includes two steps (Walsh, 2003; Jornitz and Meltzer, 2007):
1) Upstream processing, corresponding to the fermentation process where the API is produced;
2) Downstream processing, where the API is separated and purified.
A typical flow diagram of a biotechnological based pharmaceutical process is presented in Figure 1.

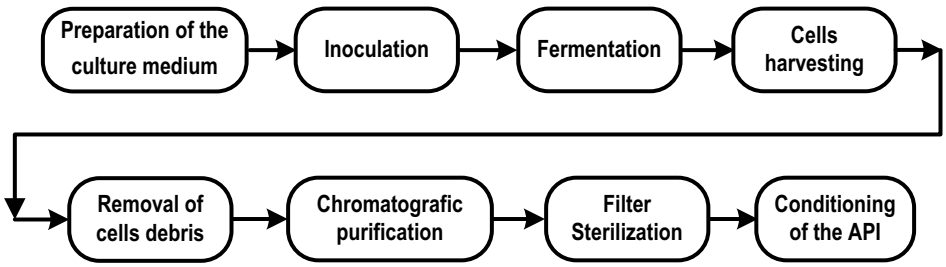

Figure 1: Primary processing for fermentation based process.

Depending upon the microorganisms' species or strains to be used, the optimum culture medium composition and fermentation conditions are previously determined to ensure an adequate cell growth and the API production (Walsh, 2003). The culture medium is previously sterilized to avoid biological contaminations and then added to the fermentator. A small portion of microorganisms (taken from a cell bank) is then inoculated to start the fermentation on a batch mode. Air sterilized by filtration is sparged into the tank to supply oxygen. The microorganisms are allowed to grow for a given time, enough to produce the maximum as possible quantity of API (a peptide expressed intra-cellularly), which has to be collected and purified.
The downstream processing includes in sequence, cell harvesting, protein concentration, and final purification (Parikh, 2005). In the first step, the microorganisms' are separated from the culture medium, and the cell walls are disrupted for release of its contents which includes the API. Then, the solid matter is removed from the liquid containing the API by centrifugation, although other methods can be used such as ultrafiltration. In the second step the API is concentrated and purified. This represents the most challenging and expensive step as the API concentrations are very low, it is mixed

with other molecules with similar properties, and very stringent quality and purity requirements have to be met. Size exclusion chromatography was the method selected with a previous step of ultrafiltration to reduce the volume of solution to be treated and to increase the API concentration. To facilitate the separation and protect the API, water for injection and some chemicals are added to the mixture. The operation of the chromatographic column is fully automated and computer controlled.
The final step of the primary processing consists of filter sterilization and API conditioning. The product of the purification is mixed with a certain volume of a non-inhibitory solution and then passed through a sterile membrane filter of nanometre's size, thus removing any biological and particle contamination (Jornitz and Meltzer, 2007). A quality control step is performed at the end of this stage, to ensure that the API is in good conditions and the resulting product is sterile (Parikh, 2005).

2.2 Secondary processing

The secondary processing includes the final product formulation (Parikh, 2005). The following steps are considered, many of them typical in most pharmaceutical processes:
1) Addition of various excipients, to stabilize and/or enhance the final product performance, and vial filling and closing;
2) Freeze-drying of the product;
3) Final product manufacture and quality control.
Figure 2 details all the relevant secondary processing steps, which are fully automated and performed in a sterile and clean environment.

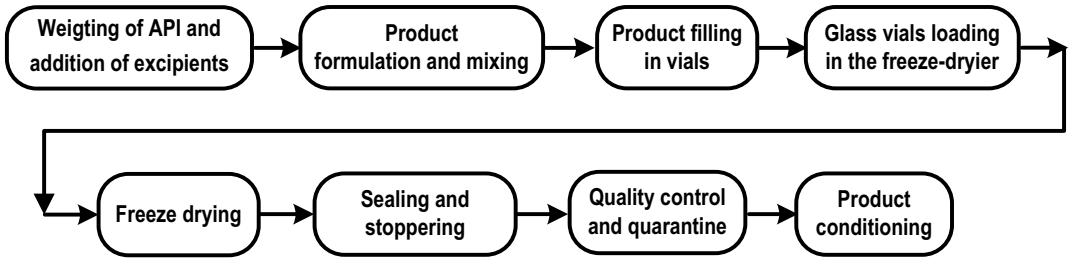

Figure 2: Secondary processing for the manufacture of lyophilized products

The final product contains both the API in the therapeutic dosage and excipients added to protect the API during its packaging, transportation and storage, to facilitate its final administration to patients, and to potentiate its beneficial action. All pieces of equipment and package parts are initially sterilized using steam and autoclaved. The vials with the final product are then passed through a freeze drying process where the liquid product is converted to a powder with low water content by the application of vacuum at mild temperatures not exceeding 30 ºC. Although expensive, this process ensures that the final product has sufficient stability for distribution and storage (Parikh, 2005), reducing the API degradation and consequent product loss. The sealing and stoppering of the vials occurs in a chamber within vacuum or neutral conditions. Water, oxygen, light, and contaminants are carefully monitored and controlled. The final steps deal with quality control, quarantine, and final storage of the injectable drug. A battery of tests is done on the final product samples, in a certified laboratory, to ensure that the final product is safe, stable, i.e. does not change if subjected to perturbations during storage and transportation, and remains active till it is administered to a patient (Jornitz and Meltzer, 2007). Failure to meet specifications or non-compliance with the approved process leads to immediate quarantine of the material until the cause of the event is ascertained. Then, containers and closures, shall be stored under quarantine until they have been tested or examined, and if deemed as appropriate they are released for usage, otherwise they are destroyed. If approved, the final product is kept in cold storage.

2.3 Auxiliary operations

The primary and secondary processing use a set of common operations that serve particular purposes. These include heat sterilization, water treatment and supply, residues collection and management and energy and heat generation. The water treatment system has two main goals: to recycle as much as

possible of the water used in the manufacturing, and to provide fresh water for the process by purifying the rain water collected by the company. In the main production processes different types of water are used with different purity requirements (from simple tap water to ultra-purified water). Depending on the water source and final use, different treatment processes are considered to fulfil the purity requirements. A purge is also present in the water system, to avoid contaminants build-up. After treatment some water is conducted to the boiler where it is heated to produce steam. Heat and steam sterilization is responsible for processing the solid and some liquid wastes, with the goals of rendering them inert and eliminate any potential biological contamination. It is based on an autoclave that receives the wastes and processes them using steam. The inert matter is then taken outside the manufacturing plant, while the water used to heat the system is piped to the water treatment system. The energy, heat generation, and cooling needs are based on a tri-generation process, the most complex auxiliary process, of which a full description is outside the scope of this article.

3. Outline of the LCA tool

The LCA tool presented in this work is based on the software MS Excel^{TM} since its front-end structure, and database, calculation, graphical and programming abilities make it an excellent development and computational software for LCA studies. Since the modelling and calculation procedures are completely open, corrections or changes to the process descriptions or models for the PEI evaluation can be easily done.

The tool can be used both in the design or improvement/retrofitting of a process. The LCA methodology as described by ISO 14040 (2006) standard was considered for its development. In the current version the tool is capable of performing a GTG analysis of the API production via a biotechnological route and the formulation of the final product, a lyophilized injectable drug, which consists of the stages marked in white in Figure 3. Although specific to a particular process, it is expected that its adaptation to other pharmaceutical processes to be quite straightforward.

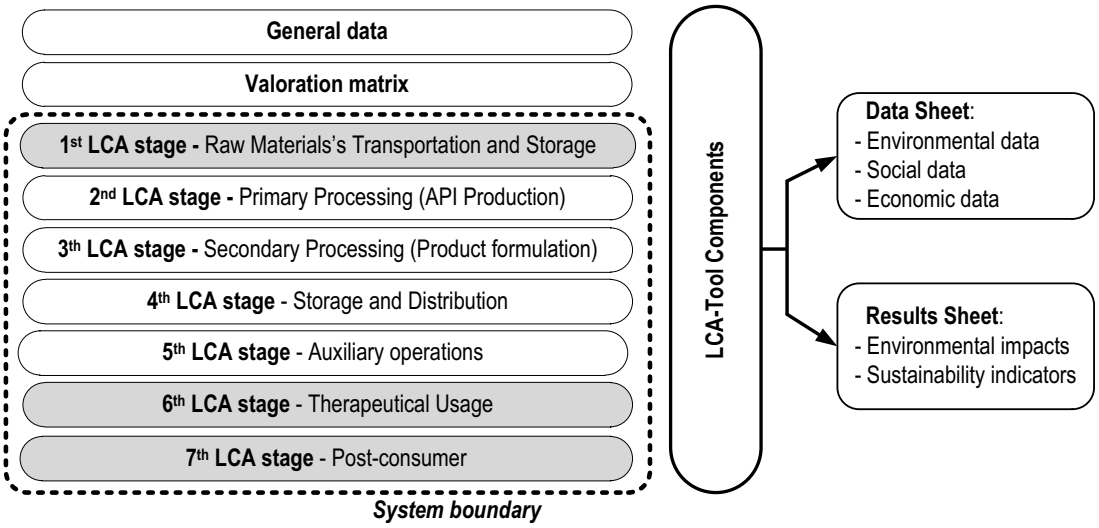

Figure 3: General structure of the LCA Tool including the life cycle stages of a pharmaceutical product

The remaining stages, extraction and processing of raw materials, raw materials transportation and storage, product consumption and its final disposal, as well as all the transportation associated (shown as grey boxes in Figure 3) are not considered in the current version of the tool. Usually these stages are not controlled by the pharmaceutical companies, since they depend on specific storage and application conditions of the products, their therapeutic application, and hospital waste management practices, among other factors. Also, the PEI associated with the equipment construction and their final decommissioning, including material disposal and recycling, are not included. Since the LCA tool is a

work in progress in further versions some of these aspects can be considered whenever relevant data and process information is available.
In Figure 3 it is clear the modular philosophy considered in the development of the LCA tool. Each module has one or several dedicated worksheets, where all the relevant inventory data pertinent to each life cycle stage can be inputted. Based on those direct inputs and outputs, i.e. the "inventory analysis data sheets", the PEI of each stage or of the overall system can be calculated after defining which impact categories are significant and what are the calculation parameters, in particular for the impact factors, defined in a special worksheet named "Valorisation matrix". In the current version the CML (Centrum voor Milieukunde Leiden) methodology, developed by the Institute of Environmental Sciences of the University of Leiden, was considered for the calculation of the PEI.
Besides the PEI the LCA tool also includes the economic and social aspects associated with the processing of pharmaceutical products. Hence it can be seen more as sustainability assessment tool than just only an LCA tool. Therefore, the "Data Sheet" and "Results Sheet" presents the relevant environmental categories and the sustainability indicators, both using numerical values and graphical representations.

4. LCA tool to perform sustainability evaluations based on indicators

For the LCA tool to be able to perform sustainability evaluations of pharmaceutical products and/or processes, one has to first identify the potential environmental, economic, and societal impacts throughout their supply chain, which was done in this work based on an extensive literature review. Then, based on the identification of the potential impacts and on the practitioner's knowledge of the system, the most significant indicators can be selected as exemplified by Mata et al. (2011) and Martins et al. (2007), by constructing a Table to evaluate the relative importance (significance or insignificance) of each potential impact. Table 1 shows the indicators selected for the present case, which can also be used to perform sustainability evaluations of other pharmaceutical processes.

Table 1: Indicators for sustainability evaluations in the pharmaceutical industry

Indicator	Unit	Description
Energy intensity	MJ/vial*	Total energy consumed in the production of one vial (can be calculated as the GTG or as the life cycle energy intensity).
Process material intensity	kg/vial	Total amount of non-renewable resources needed to obtain a unit mass of product (e.g. raw materials, solvents, and other ingredients used GTG and may be disaggregated by type of material).
Process water intensity	L/vial	Total amount of water required to obtain a unit mass of product (e.g. water for injection, purified water, and pure steam used GTG).
Potential chemical risk	-	Potential risk to human health associated with manipulation, storage, and use of hazardous chemical compounds (connotes the process safety).
Carbon footprint	kg CO_2-eq/ vial	Potential contribution of different GHG (greenhouse gas) emissions (e.g. CO_2, CH_4, N_2O) to global warming (calculated as the net GHG emissions).
Freshwater aquatic toxicity	kg 1,4-dichlorobenzene - eq/vial	Measures the impact of substances emitted to the aquatic environment during manufacture activities.
Net cash flow generated	€/vial	It equals cash receipts minus cash payments over a given period of time; or equivalently, net profit plus amounts charged off for depreciation, depletion, and amortization (a measure of the company's financial health).
Direct employment	persons/ vial	Number of persons involved in the pharmaceutical product manufacture per unit of product.

* vial is a relatively small glass bottle used to store the medication.

The energy intensity, process material intensity, and the potential chemical risk are 3D indicators as explained by Martins et al. (2007). Carbon footprint (or contribution to global warming) is a 2D indicator, as explained by Mata et al. (2011). Process water intensity, freshwater aquatic eco-toxicity, net cash flow generated, and direct employment, are considered one dimensional (1D) indicators, where the first two are environmental indicators and the third and fourth ones are economic indicators.

5. Conclusions

This article presents an Excel based LCA tool specifically designed for pharmaceutical processes, in particular the biotechnological based ones. The tool is still under development, but its results are already being used in the design and implementation of a biopharmaceutical API production process. Although it considers a GTG analysis, in the future it will be extended to broaden the system boundary. Also, its application scope can be extended to other pharmaceutical processes, in particular those based on chemical or biological routes.

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