LEADING PHARMACEUTICAL DEVELOPMENT IN A SUSTAINABLE WAY – SKYEPHARMA'S EXAMPLE

In this article, Aline Moulin, PhD, Pharmaceutical Development Director, and Laurent Rigaudeau, PharmD, Business Development and Marketing Director, both of Skyepharma, discuss how the company fulfils its sustainable development policy through its technologies and processes.

At Skyepharma, sustainable development is not just a buzzword, but a way of working that is perfectly integrated all along the value chain as early as the business development policy and deeply anchored into the corporate culture.

SKYEPHARMA ANCHORS SUSTAINABLE DEVELOPMENT IN ITS CORPORATE CULTURE

At Skyepharma it was chosen not to entrust the lead of the sustainable development policy to the HR/HSE department, as is the case in most industrial groups, but instead to entrust this leadership to a transversal working group made up of employees who have volunteered.

A sustainable development committee was set up under the impetus of the site's management and a call for volunteers was a great success; more than 15 volunteers responded to the call to devote one day each month to work on projects related to the sustainable development of the site. Their mission: to make concrete project proposals to the site's management committee in connection with the sustainable development of the site, and to carry them out. Two or three people are dedicated to each project, with specific timelines, reporting and associated budget (Figure 1).

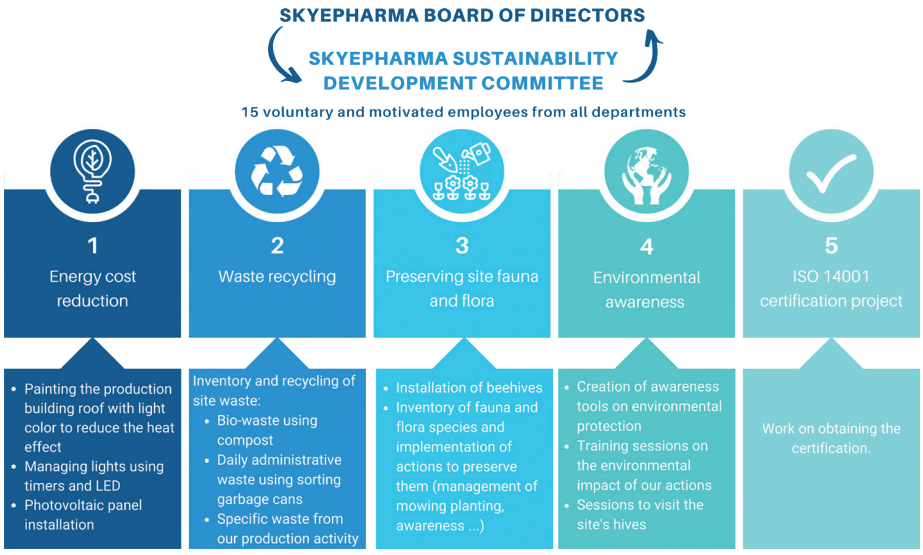

Figure 1: Skyepharma's sustainability development committee.

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Figure 2: Particle size before the use of Microfluidizer technology: 100 µm.

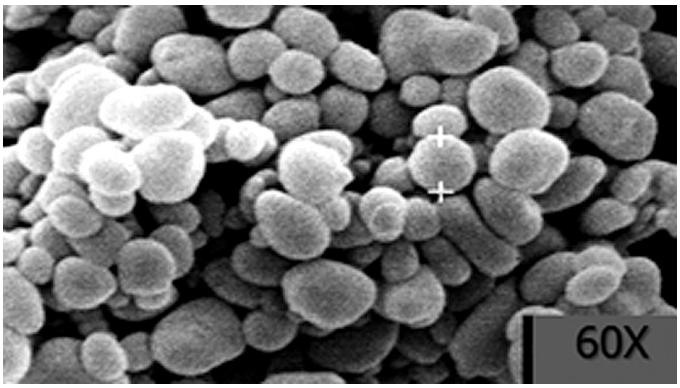

Figure 3: Particle size obtained with Microfluidizer technology: 500 nm.

All these projects are evaluated following full compliance with GMP regulations, in particular pest control. Of course, these action projects have an economic impact with substantial savings, and also a direct impact on the quality of life in the workplace and on the attractiveness of the company to new employees, who in general, not only the younger ones, are increasingly sensitive to sustainable development. This proactive policy enables the company to attract and retain the best talent to serve its clients and their projects.

SKYEPHARMA MAKES ITS OPERATIONS AND PRODUCTS MORE SUSTAINABLE

Supply Chain Policy

Skyepharma is able to use eco-friendly packaging made from sugarcane. This sustainable packaging can be handled by the company's automatic bottle line without any additional fees for same format. These bottles are fully recyclable.

Early Stage Formulation Development: From the Improvement of the API Bioavailability to the Use of Specific Drug Delivery System Technologies

The design of sustainable pharmaceuticals starts at the formulation design stage. This can go through two main steps: the improvement of the bioavailability of the active ingredient by specific techniques and the use of adapted technologies allowing a targeted release. Indeed, by allowing the use of lower, better administered doses (at the right time, in the right place), and by promoting better compliance by the patient, drug delivery systems are an excellent means to move towards more sustainable drugs by reducing drug intake.

Technology	Examples Of Technical Challenge Met	Track Record
GEOMATRIX®	• Once- or twice-daily dosing • Rapid onset followed by sustained duration • Several drugs released at different times / rates in single dose form • Absorption of drugs in lower GI tract	• Nine products on the market • Approximately three early-stage development projects per year
GEOCLOCK®	• Minimisation of side-effects at certain times of day • Drug effect at predetermined time after administration • Delivery to colon where absorption is high, or for local effect	• One product on the market • Approximately two early-stage development projects per year
SOCTEC®	• Delivery to narrow absorption window or local action in stomach	• Several clinical phase projects

Table 1: Skyepharma's technologies for modified-release applications.

Skyepharma has developed different technologies that help its clients target these two challenges.

The first is the use of Microfluidizer® technology to improve the bioavailability of the active ingredients. This technology consists of a dynamic high-pressure process where two liquid streams, solution or suspension, pass through micro-channels towards an impingement area through which the fluids flow and interact. The obtained liquid solution, or suspension, is then sprayed on a neutral support to remove the solvents and produce a dried particulate system, ready for compression. Microfluidization, followed by a drying step, can be used to improve solubility, and thus bioavailability, of poorly soluble APIs.[1]

Indeed, in most cases, new drugs that are currently being developed have poor water solubility (BCS II and IV compounds). Such limited aqueous solubility is one of the major hurdles in the development of oral-dosage forms, thus leading to high dosage strength and use of high quantity of expensive and hard to synthesise material. Figures 2 and 3 show an example of results obtained with Microfluidizer® technology: micrometre to sub-micrometre particle size with narrow size distribution.

The second type of technologies developed to help to the design of more sustainable drugs are complex oral dosage forms grouped under the names of Geomatrix®, Geoclock® and Soctec®. These have been described in previous literature[2] and are able to meet a wide range of challenges, as summarised in Table 1.

Quality by Design Approach in Development Strategy

A critical stage of development, during which a sustainable approach takes on its full meaning, is the scale up and industrialisation stage. To rise to this

challenge, Skyepharma has developed a systematic Quality by Design approach that allows it to obtain very good results in terms of reducing the risks associated with scale up, reducing costs and development time, and also reducing the quantities of materials and waste generated and the energy consumed.

Skyepharma's general methodology is a four-step process (Figure 4):

- Global risk assessment on the whole process, using FMEA as a tool, determining which is the most critical process step
- Fault tree analysis to determine the potential critical process parameters having an impact on the critical quality attributes
- Determination and quantification of the influence of each of the CPP previously identifies on the CQA, thanks to a Design of Experiment approach
- Determination of the process design space.

In previous development projects, one of the critical stages Skypharma has studied is the compression stage. A key tool used to perform such studies on the compression step is STYL'One Evolution (Medelpharm, Beynost, France) compression simulator, which allows for design of experiments (DOE) to be performed at laboratory scale, while having excellent correlations with industrial equipment.[3]

The comparison of material quantities and time required to perform the operations on an industrial press, and on the compression simulator, are shown for a typical size batch in Table 2. It can be seen that the time needed for the operations is divided by seven and the quantities of raw materials and waste is divided by more than 220. The energy required is divided by 10.

Taking the example of an 11 assay DOE, 70–95% savings in terms of raw material, associated waste, time and energy are obtained.

Of course, this has an impact on commercial performance – it enables more rapid and less costly developments compared with market standards – and also

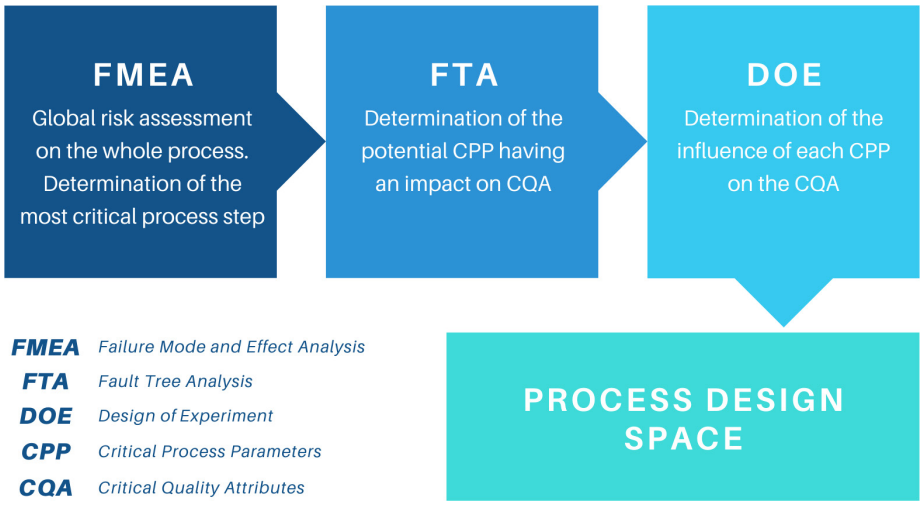

Figure 4: Quality by Design methodology.

"Sustainable production is the last, but not least, step of the development cycle of sustainable drug products."

on performance in terms of environmental impact and sustainable development.

Industrial Operation Policy

Sustainable production is the last, but not least, step of the development cycle of sustainable drug products. This requires the implementation of a continuous improvement plan in terms of energy savings, waste and effluent management, but also, above all, a state of mind that must be deeply rooted in the corporate culture.

ABOUT THE COMPANY

Skyepharma is an expert CDMO which specialises in formulating, developing and

STEP	BATCH SIZE (kg)		TIME (h)	
	Industrial Press	Simulator	Industrial Press	Simulator
Tool assembly	-	-	5	0.5
Setting of comp parameters	1	0.05	1	0.5
Production of trial batch	33	0.1	2	1
Disassembly and cleaning	-	-	20	2
Total	34	0.15	28	4
TOTAL SAVING	33		3 x shifts	

Table 2: Time and materials saving using compression simulator.

producing complex oral dosage forms, with complex and tailor-made modified-release profiles. The Skyepharma site offers a full range of services, from early stage development to industrial manufacturing and packaging. The scientific expert team, supported by patented technologies, has a solid track-record of successful development, reformulation and transfer projects. The FDA-approved GMP site in France serves worldwide customers with a recognised high level of service.

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ABOUT THE AUTHORS

Aline Moulin, PhD, graduated from the National Graduate Chemistry School of Montpellier (France) and received her MSc in Biomolecular Chemistry from the University of Montpellier in 2004. She then achieved her PhD at the Institut des Biomolécules Max Mousseron in Montpellier. She was appointed Medicinal Chemistry Research Scientist in 2007 at Sanofi Research Center (Vitry sur Seine, France). She joined Flamel Technologies (now Avadel Pharmaceuticals, Venissieux, France) R&D team in 2009 to work on the design, development and industrialisation of drug delivery systems. In 2018, Dr Moulin joined Skyepharma as Senior Project Manager and was appointed Pharmaceutical Development Director in 2020.

Laurent Rigaudeau, PharmD, graduated from the Paris Descartes University (Paris, France) and received his MSc In Production and Pharmaceutical Control from INP Toulouse in 2001. He joined Famar Group (Athens, Greece) in 2004 as Production Manager and then worked in various positions in pharmaceutical operations. Dr Rigaudeau then joined the Business Development Management Team at Famar Group in 2015, and was then appointed Business Unit Head and Site Director at Famar L'Aigle (France) pharmaceutical production site in 2019. He joined Skyepharma as Business Development and Marketing Director in June 2020.