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Embedding Sustainability into Process Development: Glaxosmithkline's Experiences

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ABSTRACT GlaxoSmithKline (GSK) aspires to be a sustainable company and has developed a series of tools and processes to apply Green Chemistry and Engineering principles to new product development. These tools and processes are used routinely to design-out hazardous chemicals, and bring products to market more cost effectively as we believe more sustainable practices will enable GSK to produce medicines with greater efficiency in mass and energy utilization.

The Eco-Design toolkit is currently composed of five modules: Green Chemistry/Technology Guide; Materials Selection Guides; FLASC™ (Fast Lifecycle Assessment for Synthetic Chemistry); Green Packaging Guide; and a Chemicals Legislation Guide. In addition, GSK has developed an EHS Milestone

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Aligned Process to ensure EHS and Sustainability are integrated into each phase of new product development. These tools and processes are designed to help scientists and engineers consider potential EHS and sustainability impacts from the manufacture of the raw materials through to the ultimate fate of products and wastes in the environment. In this paper, we will describe at a high-level some of these tools and processes. Examples of practical applications and some of their benefits to the company will also be covered.

KEYWORDS *Sustainability, Pharmaceuticals, New Process, Green Chemistry, New Process Development*

Introduction

GlaxoSmithKline (GSK) embraces sustainability as a driver for achieving competitive advantage as a leading Pharmaceutical company. To facilitate this move towards more sustainable practices, GSK has developed the Eco-Design toolkit which enables scientists and engineers to identify process improvements and address Environment, Health and Safety (EHS) issues early in the product development process.

In addition, an Environment, Health and Safety Milestone Aligned Process (EHS MAP) was developed to ensure EHS and Sustainability aspects are considered at each phase of new product development. These tools and processes enable consideration of EHS impacts from the manufacture of the raw materials through to the ultimate fate of products and wastes in the environment. Implementing practices from the Toolkit will enable GSK to produce medicines with fewer EHS impacts throughout their life cycle.

The Eco-Design Toolkit

The Eco-Design Toolkit was developed using state-of-the-art scientific advancements and standards in Green Chemistry, Green Technology and Life Cycle Assessment to assist chemists and engineers in designing-out hazardous chemicals while bringing products to market more cost effectively (Constable *et. al*., 2005).

The toolkit is accessible through the GSK intranet and is currently composed of five modules: Green Chemistry/Technology Guide, Material Selection Guides, FLASC™ (Fast Lifecycle Assessment for Synthetic Chemistry); Green Packaging Guide; and a Chemicals Legislation Guide (CLG). The combination of these tools helps to ensure that all EHS impacts are considered across a range of disciplines and phases of development. For example, using FLASC™ ensures that the life cycle impacts of chemicals used in syntheses while the CLG is used to identify chemicals of concern for each pilot plant campaign from the earliest 1 kg makes to multi-kilo production.

The Eco-Design Toolkit continues to be updated to integrate scientific advances. Currently, about 50 additional solvents have been added to the solvent selection guide and there is ongoing work to identify replacements for chemicals of concern (e.g. dichloromethane, N,N-dimethyl formamide) using computer modeling methodologies. We are also working to identify solvents that can be derived from renewable sources. Each module of the Eco-Design toolkit is described in the paragraphs below.

Green Chemistry and Technology Guide

The Green Chemistry/Technology Guide (Figure 1) offers guidance to GlaxoSmithKline scientists and engineers on how the application of Green Chemistry concepts can enable more efficient use of resources, reduce environment, health and safety impacts, reduce the use of toxic materials, and minimize costs. It includes:

- a ranking and summary of the most used chemistries and 'best-in-class' examples from well-developed GlaxoSmithKline chemical synthetic processes (Curzons *et. al.*, 2001; Constable *et. al.*, 2002)
- an EHS ranking and summary of common technology alternatives for chemical processing to improve the use of resources and minimize life cycle impacts (Jiménez-González *et. al.*, 2001; Jiménez-González *et. al.*, 2002).
- guidance on materials, process alternatives, synthetic route strategies and metrics for evaluating chemistries, technologies and processes
- a ranking and review of issues encountered during process design and development

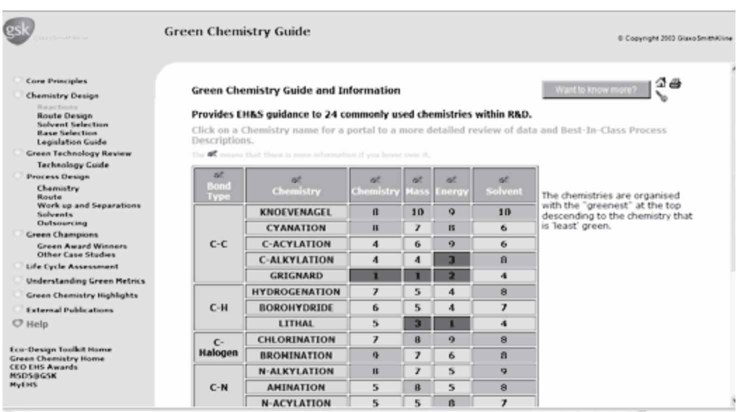

FIGURE 1
Screenshot of the green chemistry guide

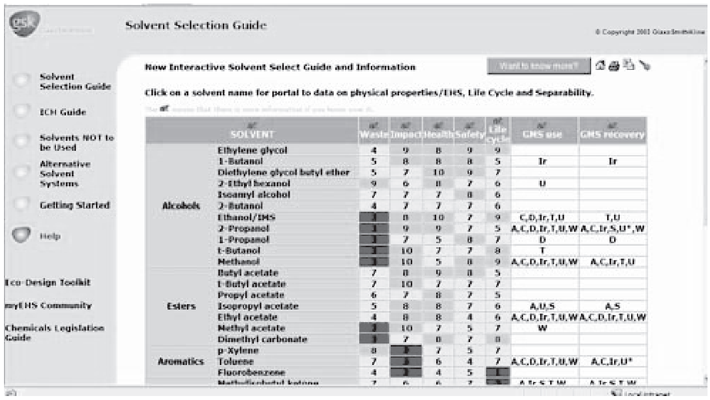

FIGURE 2
Screenshot of the solvent selection guide

Material Selection Guides: Solvents and Bases

Given the important role that solvents have in the environmental footprint of pharmaceuticals (Jiménez-González *et. al.*, 2004; Constable *et. al.*, 2007), one of the first tools developed was the Solvent Selection Guide (Curzons *et. al.*, 1999). The Solvent Selection Guide (Figure 2) contains information on a wide range of solvents used within GSK and identifies solvents that should be avoided. It allows for the selection solvents with fewer EHS impacts and:

- compares and ranks solvents according to waste profile (treatability), environmental impact (eco-toxicity), safety profile (e.g. flamability, explosivity) and health impact (toxicity)
- provides information on potential alternatives to organic solvents, such as solvent-less reactions, water and aqueous systems, carbon dioxide and other supercritical fluids.
- assesses the life cycle impacts associated with solvent manufacture to stress solvent minimization and recycling (Jiménez-González *et. al.*, 2005)
- provides information on boiling point and azeotrope formation to assist in the selection of separable co-solvents to minimize energy required for separation and treatment.
- provides detailed information on physical properties.

The Base Selection Guide builds on the success of the solvent selection guide (Constable *et. al.,* 2005). Requested by R&D chemists, the base selection guide contains information on a wide range of chemical bases used within GlaxoSmithKline R&D and manufacturing operations. It

- compares and ranks 42 bases routinely used by R&D chemists according to their environmental waste profile, environmental impact, safety profile and health impact
- provides detailed information on physical properties and EHS issues

As part of a continuing vision to develop additional guidance on materials, a prototype materials selection guide was developed for acids, catalysts and reducing agents.

FLASC™—Fast Life Cycle Assessment for Synthetic Chemistry

FLASC™ allows chemists to perform streamlined environmental life cycle assessments of processes and measure green metrics such as mass efficiency (Curzons *et. al,* 2007). The FLASC™ tool development was based on a full LCA of an Active Pharmaceutical Ingredient or API (Jiménez-González *et. al.*, 2004). It assesses eight different environmental life cycle impact categories associated with materials used in synthetic routes: Mass Intensity, Cummulative Energy Requirements, Global Warming Potential, Photochemical Ozone Creation Potential, Acidification, Eutrophication, Total Organic Carbon (pre-treatment) and oil and natural gas depletion for raw materials manufacture.

FLASC helps scientists and managers to rapidly identify the greenest option, from a materials use perspective by:

- comparing and benchmarking GSK synthetic processes with a color coded score (Figure 3)
- estimating the environmental life cycle impacts of the materials used

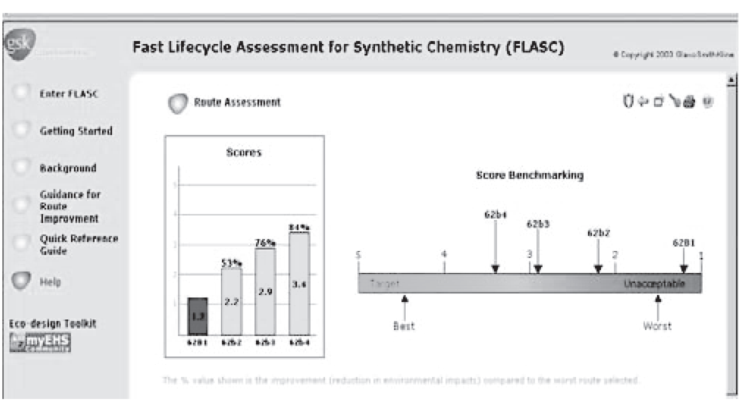

FIGURE 3
Example of an output of FLASC™

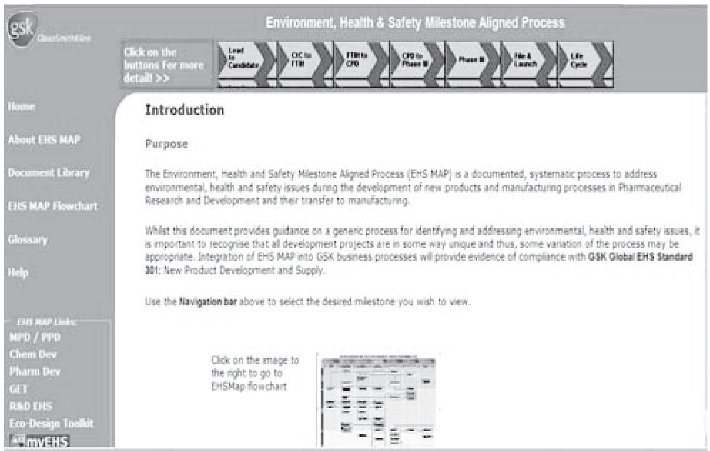

FIGURE 4
Screenshot of EHS MAP

- identifying the materials with the biggest contribution to those life cycle impacts
- providing guidance on how to reduce those impacts.

FLASC can also be used to track synthetic route or manufacturing process improvements. Additional life cycle inventory data for materials of interest to the Pharmaceutical Industry are currently being obtained for the FLASC database. These materials include key raw materials, catalysts and complex specialty chemicals. These additions broaden the scope and improve the life cycle impact estimations FLASC delivers.

Green Packaging Guide.

The Green Packaging Guide provides a packaging assessment tool, guidance and a business process for evaluating and selecting packaging options for the Pharmaceuticals and Consumer Healthcare businesses. It provides an interactive section known as WRAP — Wizard for the Rapid Assessment of Packaging. WRAP allows packaging designers and managers to rapidly assess the environmental impacts of existing and new packaging designs, including:

- benchmarking new and existing packaging designs against GlaxoSmithKline's existing product portfolio,
- a best-in-class example in each packaging category,

- green packaging guides for nutritional healthcare products and consumer healthcare products,
- a score with a simple color-coded report that clearly shows if the packaging associated with a product is better or worse than the appropriate benchmark.

WRAP also allows more detailed analysis of the underlying issues around packaging and enables users to compare alternative packaging designs through scenario analysis.

Chemical Legislation Guide.

The CLG is the Eco-Design toolkit's newest addition. While most of our tools focus on best practice and issue identification, the CLG was developed in anticipation of chemicals legislation (e.g. Homeland Security lists, CA Proposition 65, REACH) in various parts of the world to phase out high hazard substances from routine use (chemicals of concern). This provides R&D and manufacturing scientists and engineers with a user friendly tool that considers hazard, volume and phase of use to deliver targeted guidance about a variety of chemicals. Because the tool is a spreadsheet it is easy to update and requires no special training to use. Consequently, uptake of the tool has been very rapid and implementation was almost immediate.

Environment, Health and Safety Milestone Aligned Process. EHS MAP

EHS MAP is a documented, systematic process to address EHS and Sustainability aspects during the development of new products and manufacturing processes in Pharmaceutical Research and Development and their transfer to Manufacturing facilities.

The EHS MAP Process is integral to GSK business processes and aligned with new product development and supply milestones; identifying responsibilities, accountabilities, deliverables and communications. To embed Sustainability principles into new product development, EHS MAP enables the identification of activities that can improve process efficiencies, eliminate waste and facilitate the new product development and supply process;

The outputs of the EHS MAP process are a better understanding and appreciation of EHS and Sustainability throughout a products life cycle; the implementation of best practices throughout the company; and finally having people across the company engaged and committed to making

EHS and Sustainability an integral part of new product development and supply.

Examples of Applications and Benefits.

The Eco-Design toolkit and EHS MAP are routinely used in GlaxoSmithKline, primarily to support new product development. Their utilization has rendered many tangible results that enable GSK to drive towards more sustainable practices. Some examples of success of this operational sustainability are described below:

1. Green chemistry metrics have been adopted by and integrated into R&D Chemical Development evaluations of pilot plant campaigns. These metrics are used by chemists and engineers to eliminate toxic materials and to reduce material consumption and waste.
2. Life cycle impacts and chemicals of concern (hazardous chemicals) are identified in pilot plant campaigns and plans are set to improve the environmental profile as the process progresses through the development milestones. For instance, during 2008, the mass percent of chemicals of concern decreased 9-fold (Figure 5) and estimated average life cycle impacts were reduced 4-fold as compounds moved to the last stage of development (Figure 6).
3. More than 500 life cycle assessments of synthetic routes have been performed using FLASC in R&D and Primary Manufacturing.

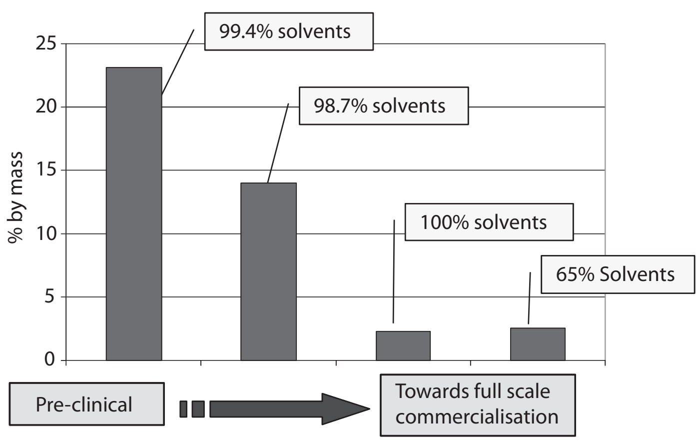

FIGURE 5
Materials of concern in the 2008 portfolio

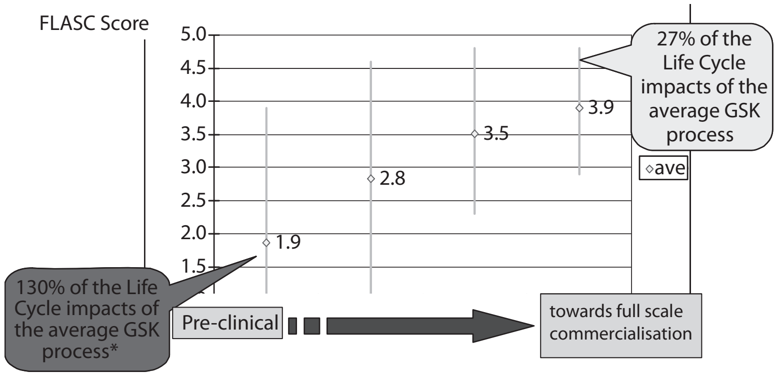

FIGURE 6
Life cycle Impacts on the 2008 development portfolio. The average performance of the benchmark routes (1990–2000) was assigned a FLASC score of 2.3

4. A target has been set to double the average mass efficiency of processes for new products introduced between 2006 and 2010. There is already progress in this area, such as the manufacturing route for a development compound; which compared to the previous route it eliminated several hazardous chemicals, halved estimated life cycle impacts, and doubled the mass efficiency (Table 1). This work won the 2nd place in the Green Chemistry category of GlaxoSmithKline CEO's EHS Excellence Awards in 2005.
5. The solvent selection guide is widely used in GSK facilities throughout the world and it has been integrated into other solvent selection tools in R&D. To promote a spirit of collaboration, the solvent guide has been shared within collaborative consortiums.
6. The work to identify replacement for chemicals of concern (e.g. dichloromethane, N,N-dimethyl formamide) using computer modeling methodologies developed to identify solvents that would provide the same process performance with a smaller impact (Gani *et. al*, 2005, Gani *et. al.*, 2006) has been verified in initial laboratory experiments and proved that an alternative solvent not only provided a better environmental profile, but improved process performance.

TABLE 1
Comparison of Selected Green Metrics for Two Routes of a Development Compound

Route	No. of Steps	Mass Intensity (kg/kg product)	Mass Efficiency (%)	Solvent Intensity (kg/kg product)
F (old)	6	162	0.6 %	99
G (new)	3	61	1.6 %	36

7. WRAP is used to perform assessments of environmental benefits derived from reductions and improvements in packaging. A new version is currently being developed following requests from the Consumer Healthcare business.

Concluding Remarks

GlaxoSmithKline's Eco-Design toolkit and EHS MAP process are a unique-in-their-class set of tools to design safer, greener, more efficient processes by minimizing their EHS and life cycle impacts and by making sustainability an integral part of process and product design. Tools such as the Solvent Guide, FLASC or the Green Technology Guide have been first in their class and have been recognized for their innovation and for leading the green design of pharmaceuticals.

Although there are still challenges in the quest for sustainability that need to be addressed, the achievements to date are an excellent sample of GSK's vision for Operational Sustainability and its commitment to strive towards more sustainable business practices.

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