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“Discussion Document on Eco-pharmacostewardship”

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Executive Summary

Eco-pharmacostewardship of Pharmaceutical Products

The application of eco-pharmacostewardship approaches is essential at all stages in the lifecycle of pharmaceutical products (PPs) in order to minimise their environmental impact.

Leading pharmaceutical companies report on a number of stewardship methods currently in place including schemes to conserve energy and water, reduce waste and CO₂ emissions. The European Federation of Pharmaceutical Industries and Associations (EFPIA) recognises that the pharmaceutical industry has a responsibility for life cycle stewardship, however NGOs currently appear to have either a low level of awareness of, or interest in, issues surrounding the impact of PPs on the environment.

Over recent years there has been a steadily increasing drive within the pharmaceutical industry towards the synthesis of ‘greener’ PPs and the adoption of green chemistry methods and technologies. The majority of improvements have been made to the manufacturing process, however little consideration has, so far, been given to the environmental impact of PPs at end of life. Strategies should therefore be developed to limit the potential harm of pharmaceuticals on the environment including development of more efficient wastewater treatment technologies, and development of PPs that are benign by design or designed for biodegradability. The implementation of tax and other incentives could make these eco-pharmacostewardship approaches more attractive to pharmaceutical companies and hence increase their uptake.

When assessing the sustainability implications of both new and existing PPs, it is important to take into account each stage in their lifecycle. Although numerous methods have been developed and applied to assess the sustainability implications of PPs, there is no standardisation of these methods as their application is voluntary. The methods applied by the pharmaceutical industry also do not tend to incorporate product ‘use’ and ‘fate’ issues, which are essential to gain a true estimate of sustainability implications of PPs. In addition, companies must ensure they have a good understanding and control of their supply chains, in particular in light of outsourcing, to ensure processes are truly green.

The most comprehensive existing classification and labelling scheme for PPs is running in Sweden. This voluntary scheme targets active pharmaceutical substances and information on their environmental impacts is made publicly available on websites and in information booklets, but not via labels on drug packaging. The extension of a model similar to the Swedish scheme could potentially be desirable on a European level. Considerations for introducing eco-labels for PPs remain theoretical to date. Key issues for developing and implementing classification & labelling schemes include the standardisation of the information used, the criteria applied, who provides the information and mode of communication.

In Europe, drug take back schemes of unused/expired medication are an obligatory post-pharmacy stewardship approach for reducing the discharge of PPs into environmental waters. Although the contribution of improper disposal of PPs to the overall environmental burden is not well understood and generally believed to be minor, drug take back schemes are still considered to be important. High levels of public awareness and education on the environmental consequences of the disposal of unused/expired drugs are key for the success of such schemes.

To ensure maximum effectiveness of eco-pharmacostewardship approaches, engaging key stakeholders across the PP lifecycle is essential. This can be done by communication methods of good practice and providing relevant and practical information on the environmental impacts of PPs to manufacturers, prescribers and users of pharmaceuticals. Education and training of professionals is also of great importance.

The eco-pharmacostewardship approaches identified via the KNAPPE project should be taken into consideration when developing new PPs to lead to the development of a new generation of green and sustainable pharmaceutical products. It is essential that they have as few adverse effects as possible, whilst at the same time maximising their beneficial effects. Based upon the findings of this study, the KNAPPE project has compiled a list of recommendations for the increased development of greener PPs. KNAPPE has also proposed key eco-compatibility criteria to score PPs on their environmental impact at all stages of their life cycle, which could be the basis of a new classification and labelling scheme for PPs.

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STATUS, CONFIDENTIALITY AND ACCESSIBILITY							
Status			Confidentiality			Accessibility	
S0	Approved/Released		R0	General public		Work-space	
S1	Reviewed		R1	Restricted to SWIFT6WFD members		Internet	
S2	Pending for review		R2	Restricted to European. Commission	x	Paper	x
S3	Draft for comments						
S4	Under preparation	x					

1. Introduction

Can the impacts of Pharmaceutical Products (PPs) on the environment be reduced through the use of eco-pharmacostewardship approaches including the use of clean synthesis, classification and labelling and better communication of methods of good practice?

This discussion document seeks to explore ways in which the impact of PPs on the environment can be reduced at all stages in their lifecycle (production, prescription, use and disposal) through the use of eco-pharmacostewardship approaches. To achieve this the discussion document provides:

- A review of the potential role and significance of eco-pharmacostewardship over the lifecycle of PPs;
- An understanding of how and where stewardship schemes can be adopted to improve the overall sustainability of PPs;
- Identification of existing examples of good practice and drivers for increased uptake.

Information has been drawn from current scientific literature, national and international reports as well as consultations with key stakeholders. Key issues are highlighted throughout the document to stimulate discussion around this important issue. Strategies and recommendations for future actions are also proposed for the increased development of greener PPs.

2. The Application of Eco-pharmacostewardship Approaches to Minimise the Environmental Impacts of PPs Throughout their Lifecycle

The impact of pharmaceutical products on the environment is not limited to end-of-life. To manage these impacts eco-pharmacostewardship approaches must be applied at all stages in the lifecycle of a PP. Companies engaged in chemical manufacturing are facing increasing societal demands to reduce their environmental footprint. This section seeks to identify what eco-pharmacostewardship approaches are currently being applied by the pharmaceutical industry and other relevant organisations to minimise the environmental impacts of PPs throughout their lifecycle, as well as suggesting other approaches that could be adopted in future.

2.1 Existing Approaches Made by Major Pharmaceutical Companies

Seventeen leading pharmaceutical companies were identified and publicly available documents produced by each company were analysed to determine what approaches are in place to minimise the impact of pharmaceutical products throughout their life cycle. These approaches included general environmental impact reduction schemes, as the whole life cycle of the pharmaceutical products were considered.

The approaches outlined in these documents are summarised in Table 2.1. (This table provides an overview of the approaches and is not meant to be an environmental grading system because it reports only the environmental stewardship approaches that are publicly reported). The table reveals that all companies identified are attempting to reduce their environmental footprint and thus minimise the environmental impacts of PPs throughout their life cycle. However, approaches differ in sophistication. Most companies report steps to minimise landfill of hazardous substances. Roche takes this further by adopting a clean soil approach, which encompasses both a reduction in soil contamination from landfill of hazardous waste and the identification of soil and groundwater contamination caused by site operations.¹ Several companies report the implementation of green chemistry. AstraZeneca also reports the foundation of a green chemistry network, which links environmental specialists to help promote the principles of green chemistry and

engineering.² Some of the companies, such as Roche, report the implementation of green packaging, which seeks to minimise the quantity of packaging materials used and promotes the use of packaging materials with favourable properties (eco-balance, safety, potential for re-use and recycling).¹ It is interesting to note that only four companies report environmental fate and green synthesis techniques; however, the data may be influenced by companies only reporting what they perceive to be interesting to the public, which would explain why approaches that are already widely publicised as general environmental initiatives, such as CO₂ reduction and energy-saving initiatives, other initiatives that are not perceived to be as familiar to the general public, such as green chemistry and solvent use reduction, are not readily reported. Thus, the approaches reported by most companies are focused on reducing impact at the development and production stage of the pharmaceutical products' life cycle. Tucker of Pfizer Global R&D reported that 'pharmaceutical green chemistry offers an opportunity to educate the public with regard to our good environmental stewardship through operational transparency, while also detailing industrial motivations leading to greater public awareness, understanding and trust.'³ The only company that reports approaches to minimise the impact of the pharmaceutical product once it has left the factory is Eli Lilly, which reports that it is one of the leading members of Pharmaceutical Research and Manufacturers of America (PhRMA), working to provide guidance on disposal of unused products in a manner that minimises environmental impact.⁴

Companies engaged in chemical manufacturing are facing increased societal demands to reduce their environmental footprint, so the implementation of the measures mentioned above and in Table 2.1 is to be expected. However, there is a less visible group of pharmaceutical companies that may not be active in the research of new pharmaceutical compounds, but they produce generic drugs once they reach off patent status. Six generic manufacturers were investigated*, but only one, Krka, publicly reported initiatives to reduce the impact of pharmaceutical products throughout their life cycle.⁵ The approaches reported are similar to the general approaches reported by pharmaceutical research companies and include steps to reduce energy use and waste production.

* Dalton; Intas Pharmaceuticals Ltd; Krka; Pharmascience; Union Chemical and Pharmaceutical Ltd; United-Guardian, Inc

2.2 Trade Association Position on Environmental Stewardship of PPs

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the pharmaceutical industry operating in Europe. Through its membership of 32 national associations and 44 leading pharmaceutical companies, the organisation was contacted to ascertain what information they provide to their members on the issue of environmental stewardship. The report on the annual general meeting 2007 revealed no references to environmental impacts.⁶ A search of the website reveals few references to environmental impacts.⁷ However, email contact was initiated and the following responses were obtained:

- Pharmaceuticals used as human medicines can get into the environment by three distinct routes: releases during manufacturing, releases resulting from patient use and releases resulting from the disposal of unused medicines.
- It is generally agreed, that the first and last of these sources represent a very small proportion of the total, with the major input arising from therapeutic use. However, the industry recognises that it has a responsibility for life cycle stewardship and is thus involved in seeking to minimise all three types of release.
- Individual companies are already involved with their local regulators using existing legal instruments to reduce discharges of pharmaceuticals from primary and secondary manufacturing sites to levels that pose insignificant risks to the environment. Indeed most large research based companies have already established their own internal control limits in advance of any regulatory requirements. No additional regulatory instruments are needed in Europe to achieve these improvements.

Table 2.1 Publicly reported approaches to minimise the impact of pharmaceutical products on the environment by 16 leading pharmaceutical companies

Company	Energy conservation	Water conservation	General waste reduction	Hazardous waste reduction	Solvent waste reduction	Green synthesis techniques	Sound sourcing	Product packaging	Environmental fate	Green chemistry	General clean Air	CO ₂ emissions
Pfizer ⁸	✓	✓	✓	✓	✓		✓			✓	✓	✓
AstraZeneca ⁹		✓	✓	✓	✓			✓	✓	✓	✓	✓
Merck and co. ¹⁰	✓	✓	✓	✓		✓				✓	✓	✓
Wyeth ¹¹	✓	✓		✓							✓	✓
Novartis ¹²	✓	✓	✓	✓	✓				✓		✓	✓
Roche ¹³	✓	✓	✓		✓		✓	✓			✓	✓
Eli Lilly ¹⁴	✓	✓	✓	✓	✓				✓	✓	✓	✓
Bristol-Myers Squibb ¹⁵	✓	✓	✓	✓			✓	✓		✓	✓	✓
Johnson and Johnson ¹⁶	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
Novo Nordisk ¹⁷	✓	✓	✓									✓
Abbott ¹⁸	✓	✓	✓				✓					✓
Boehringer Ingelheim ¹⁹	✓	✓	✓	✓	✓	✓					✓	✓
GlaxoSmithKline ²⁰	✓	✓	✓	✓	✓			✓	✓	✓	✓	✓
Schering-Plough ²¹	✓	✓	✓	✓	✓	✓	✓				✓	✓
Lundbeck ²²	✓	✓	✓	✓	✓						✓	✓
Bayer ²³	✓	✓	✓	✓	✓		✓				✓	✓

- Unused medicines make a small contribution to the residue levels of pharmaceuticals in the environment. If the unused medicine is returned to the pharmacist or disposed into household waste that is subsequently incinerated or sent to a secure landfill site, then entry to the environment is minimal. The earlier method of disposal, by flushing into the toilet, which could result in releases to the environment, is no longer recommended. In the European Union, the recently amended Directive on human pharmaceuticals requires all Member States to establish collection systems for unused medicines. In addition the EMEA Guidance Document on Environmental Risk Assessment of human medicines recommends that for all medicines, the patient information leaflet should contain the following general statement - “Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.”
- The main route of entry for pharmaceuticals into the environment is from use by patients and subsequent excretion. The potential implications for the environment, resulting from this, are now determined, in the European Union, prior to product approval by means of a comprehensive environmental risk assessment process using a tiered testing approach. This is detailed in the EMEA Guidance.

The website of the Pharmaceutical Research and Manufacturers of America (PhRMA)²⁴ was scrutinised to determine what advice was available regarding information about stewardship approaches, but none were publicly available. However, Eli Lilly reports that it is working with PhRMA to provide guidance on disposal of unused products in a manner that minimizes environmental impact.⁴

The Swedish association of pharmacy (LIF) is making publicly information available on the environmental fate and effects of human medicines via FASS online (the Swedish doctors’ prescribing guide).²⁵ (See Section 6.1 for further information)

2.3 NGO Position on Environmental Stewardship of PPs

Over 20 NGOs were contacted to find out what stewardship approaches they were aware of that are presently implemented to minimise environmental impacts of pharmaceutical products throughout their life cycle and furthermore, what approaches could be developed to minimise these impacts (for example, product labelling regarding the disposal of unused

pharmaceutical products). However, responses were not forthcoming. Natural Resources Defence Council responded by directing attention to two links. The first link documented a general web article regarding the detection of Pharmaceutical products in river waters. The second link was an update of the Californian legislative index SB 966, which would require retailers of pharmaceutical drugs to establish a system for accepting and collecting unused medicines to be disposed of properly. This lack of response may be indicative of the lack of public awareness to the issue of eco-pharmacostewardship.

2.4 Relevant EU projects that relate to Eco-pharmacostewardship

The Management Strategies for Pharmaceuticals in Drinking Water (START) project is currently underway, which aims to integrate different sectoral measures for the reduction of pharmaceutical emissions into waterways into a systemic management strategy.²⁶ Three different approaches are to be studied:

- Technical Approach (short- to mid-term): Conventional procedures for sewage treatment and drinking water processing are largely replaced by innovative procedures (e.g. membrane filtration, reversed osmosis).
- Conduct Approach (mid- to long-term): Present prescription practices, use and disposal patterns of pharmaceuticals change towards a higher environmental sensibility.
- Agent Approach (long-term): Innovations in sustainable pharmacy lead to the substitution of problematic agents by those that are simultaneously optimised for activity in humans and degradability in the environment.

2.5 Summary

Conclusions that can be drawn from this research are as follows: Pharmaceutical companies generally report publicly recognised approaches to minimise the environmental impact of PPs throughout their life cycle however, other initiatives may be being undertaken which are not publicly acknowledged. Some of these initiatives undertaken by PhRMA include working to provide guidance on disposal of unused products in a manner that minimises environmental impact. The lack of response from NGOs suggests that minimising the impact of pharmaceutical products is not on the public agenda and is largely ignored.

Key Issues and Discussion Points

- **Could the implementation of tax incentives to make green chemistry and other stewardship approaches financially attractive encourage more pharmaceutical companies to implement measures to reduce the impact of PPs throughout their life cycle?**
- **The level of awareness of NGOs on the issue of eco-pharmacostewardship is low. NGOs could be engaged by raising public awareness of eco-pharmacostewardship as a green issue, and by raising awareness amongst NGOs of the problems associated with the presence of pharmaceutical products in aquatic ecosystems by providing them with the findings of this and other EU projects.**
- **Other stewardship approaches that could be employed to reduce the impact of PPs across their lifecycle include:**
 - **Developing a system to score PPs on their environmental impact at all stages of their development including post consumer fate.**
 - **Placing this score on PP packaging to enable the consumer to make educated environmental choices on PP consumption.**

3. Designing 'Greener' Pharmaceutical Products:

The Adoption of Benign-by-Design Clean Synthesis Methods and Green Production Technology

Green Chemistry is internationally recognised as the term to describe the development of more environmentally acceptable and sustainable chemical processes and products. Application of green chemistry in the chemical industry as a whole is fragmented. However, an increasing number of drivers exist that will strengthen the need for a greater adoption of green chemistry clean synthesis methods and technologies. These include increasing process costs (waste treatment and disposal, energy costs), increasing costs of and demand for diminishing traditional petroleum-derived raw materials and the increasingly strict legislation governing the production, storage, use and disposal of chemicals.²⁷ Some representatives of the pharmaceutical industry also believe that the new European chemicals legislation, REACH (registration, evaluation and authorisation of chemicals), which entered into force on 1st June 2007, may pose a serious threat to the supplies of a large number of pharmaceutical intermediates.²⁸

Fig. 3.1: Clean synthesis of PPs

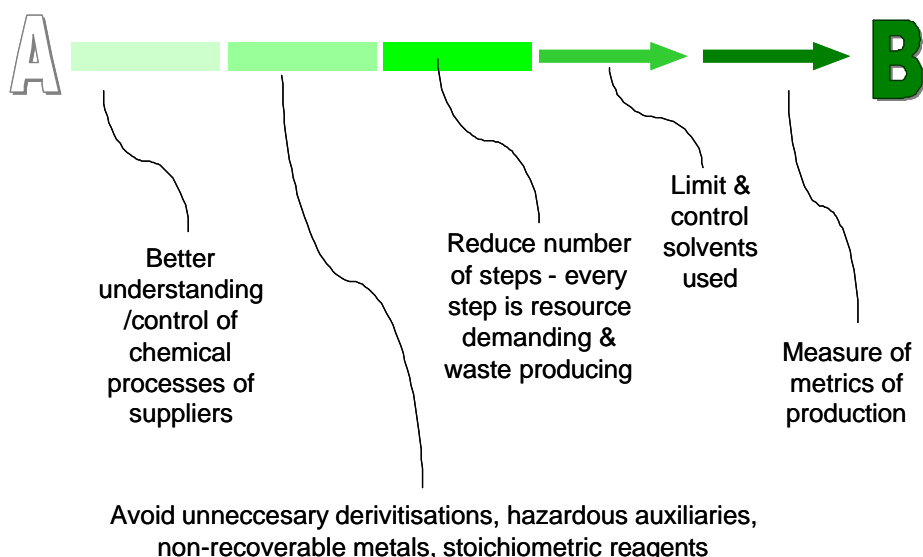


Figure 3.1 demonstrates some of the methods that can be applied in the design of 'greener' PPs. Review of available literature has revealed that benign by design clean synthesis methods and green production technologies are being adopted by the pharmaceutical industry in the syntheses of PPs to a certain extent. Some companies, including Merck and GlaxoSmithKline, have also established in-house best practice awards to reward their staff for embracing these initiatives.^{29,30}

3.1 Reducing Waste/Energy Consumption and Developing Less Hazardous Syntheses

The manufacture of PPs usually involves the use of multistage batch processes to prepare complex chemical compounds in relatively small quantities. Compared to the bulk and fine chemical industries, much higher levels of waste are produced per kilogram of product.³¹ Adoption of benign by design clean synthesis methods can improve the efficiency of the manufacture of PPs. Through a range of green chemistry techniques Pfizer improved the commercial synthesis to sildenafil citrate, used for the treatment of male erectile dysfunction, and developed a route which produced just 6Kg of waste per Kg of product (compared to the pharmaceutical industry standard of 25-100Kg).³² Eli Lilly were also successful in using green chemistry to redesign the synthesis of an anticonvulsant drug candidate leading to the elimination of 300kg of toxic chromium waste and 34,000 litres of solvent for every 100kg of product produced.³³

Avoiding unnecessary derivatisations and minimising the use of protection/deprotection steps again reduces the amount of reagents used and waste produced. In fact, reducing the overall number of synthetic steps has straightforward benefits and reduces the environmental and economic impact of the manufacturing process as every step uses resources and produces waste. Telescoping stages together can also reduce energy usage by avoiding the need to isolate intermediates³⁴ and formed part of the strategy to an eco-efficient pilot plant synthesis of some important pharmaceutical intermediates by Roche.³⁵

The percentage of PPs sold chirally pure or as a single enantiomer has grown significantly over recent years.³⁶ Another important method of reducing waste is by designing a route whereby the unwanted enantiomer can be recycled.³⁴

The development of less hazardous syntheses is also critical both from the viewpoint of worker safety during the manufacturing process and in terms of the production and hence disposal of hazardous waste. Table 5.1 shows numerous PPs where environmental improvements have been made by reducing the number of manufacturing steps e.g. Emend® and Cytovene®, improving energy efficiency e.g. Celebrex® and Accupril™, and using less hazardous syntheses e.g. LY300164 and Irbesartan®. However, a tendency in recent years to outsource many early-stage intermediate manufacturing needs to be taken into consideration: by better understanding and control of contract manufacturers' processes or by bringing more of those processes back in-house. Among the indicators that the larger pharmaceutical

companies are considering the latter is the recently published priority list of process chemistries in need of environmental improvement³⁷, which includes some processes not currently used to a significant extent by those companies in-house (e.g. fluorination and oxidation).

3.2 Catalysis

In a review from AstraZeneca on improving sustainability of the pharmaceutical industry, the development and application of catalytic methodologies are described as a powerful tool to improve both the economic and environmental profile when designing synthetic routes within process R&D.³⁸ Among the important benefits listed are the reduced usage of raw materials, solvents and reagents for the production of a given amount of product. The use of catalytic rather than stoichiometric reagents dramatically decreases the amount of waste generated and enhances the atom economy of the process (see metrics section for definition of atom economy).

In the multi-kilogram manufacture of BILN 2061, a potent HCV (Hepatitis C virus) protease inhibitor, Boehringer Ingelheim Pharmaceuticals Inc reported the development of a convergent, scalable synthesis using a highly efficient catalysed ring closing reaction (metathesis).³⁹ Metathesis reactions represent an important green synthesis method as they are more efficient, easier to use (stable under ambient conditions), and are environmentally benign (produce less waste and use non-hazardous solvents). Three scientists were awarded the Nobel Prize in chemistry in 2005 for their involvement in the development of metathesis reactions.⁴⁰ Table 1 below also highlights a number of case studies where catalysis has been used to design a greener route to PPs, including Januvia™, Lipitor®, Lyrica®, Zoloft® and Ibuprofen.

A number of past EU projects have looked at the application of catalysis as a key technology for the pharmaceutical industry. Scientists at Akzo Nobel Chemicals in the Netherlands led a EU Framework 5 project to provide training for young researchers and develop novel heterogeneous catalytic and separation technology for the creation of sustainable chemical and pharmaceutical industry processes.⁴¹ A recently completed COST Action on applied biocatalysis brought together a large multidisciplinary team to develop new stereoselective and environmentally friendly reactions catalysed by enzymes, which is of direct relevance to the synthesis of chiral drugs.⁴²

3.3 Safer Solvents/Auxiliaries and Reduction in Use

Large volumes of solvent are used in reactions, work-ups, purifications and cleaning, and solvent use is often the largest contributor to waste in the production of PPs⁴³. From a green chemistry perspective solvents should be non-hazardous, non-toxic and should be contained. Some reactions can be carried out in the absence of solvents and can be accelerated using microwave activation, which can significantly reduce energy usage.⁴⁴ However the use of microwave technology in the pharmaceutical industry tends to be limited to smaller scale laboratory synthesis although it could find future potential in scale-up.⁴⁵ The development of a prototype chemical reactor using microwave technology for the continuous production of bulk chemicals at commercial production rates was the focus of a recent EU Framework 6 project led by Surface Transforms in the UK, with the biopharmaceutical company Organon amongst the partner organisations involved.⁴⁶

Alternative reaction solvents include water, supercritical CO₂ and non-volatile ionic liquids.⁴⁷ Ionic liquids are liquid at room temperature, have negligible vapour pressure and are recyclable, which has led to a recent interest in them as green reaction media and solvents.⁴⁸ Research into the use of ionic liquids as an alternative solvent for use in nucleoside chemistry, an area important in drug discovery in particular for anti-HIV agents, has been funded by Isis Pharmaceuticals Inc.⁴⁹ Researchers in the Netherlands have also recently developed a new method to manufacture levodopa, a drug used to treat Parkinson's disease, using an ionic liquid and supercritical carbon dioxide, which they claim dramatically reduces energy and waste costs⁵⁰. Merck & Co, Inc have reported the kilogram-scale purification of pharmaceutical candidates and intermediates using preparative Supercritical Fluid Chromatography (as an alternative to HPLC). The advantages of this method include the use of carbon dioxide rather than hydrocarbon solvent, a 70-90% reduction in the overall solvent usage and improved chromatography.⁵¹

Despite these examples the use of alternative reaction media in the production of PPs has not been widespread to date. However a significant amount of effort has made towards solvent recycling, using single solvent systems and avoiding the use of chlorinated solvents.³⁴ A number of pharmaceutical companies including GSK and Pfizer have also developed in house solvent selection guides.^{52,53} This provides information on the environment, health and safety data and guidance for solvents commonly used in the pharmaceutical industry. Solvent optimisation, recovery and recycling can also play a major role in decreasing the

environmental burden of solvents. Almost all the drugs in Table 5.1 reduce the environmental burden of solvent use either by using more benign solvents, by reducing the quantities used or via recycling.

3.4 Renewable Resources

A fundamental area in green chemistry that is not widespread in the pharmaceutical industry is the use of renewable resources. Scientists at Lund University in Sweden are currently looking at the development of speciality chemicals from renewable resources, including biosurfactants for use in pharmaceutical preparations.⁵⁴ A EU Framework 4 project led by Wageningen Agricultural University in the Netherlands, in collaboration with the pharmaceutical and other industries, was carried out to explore the use of chiral terpenes derived from agro-industrial crops and waste products as renewable raw materials for the production of pharmaceutical intermediates and other products.⁵⁵ However, information on other applications is limited. The utilisation of renewable resources represents an area that could potentially be exploited in future by the industry, especially as bio-derived building block chemicals become more widely available.

3.5 Economics Benefits of Designing Greener PPs

Employment of green chemistry methods and techniques also offer financial incentives. J.L. Tucker, Associate Scientist at Pfizer R&D was quoted at the 'Applications of green Chemistry in the Pharmaceutical Industry' conference held in 2002 as saying 'Almost without exception, green synthetic techniques offer enhanced process economics'⁵⁶ using the Zolofit® synthesis as an example. AstraZeneca, GlaxoSmithKline and Pfizer also reported that project cost reductions of 50% or more have been achieved when environmental issues are addressed concurrently during the early stages of process development, as well as providing wider benefits through the use of sustainable processes and technologies that provide greater process efficiencies.³⁴

3.6. Summary

The adoption of green chemistry methods and technologies is an ongoing process and pharmaceutical companies and their partners in the chemical industry and academia should strive towards continuous improvement of synthetic methods to replace existing

environmentally undesirable reactions and processes. Process chemists and engineers must be involved in order to adapt these new methods to manufacturing-scale processes. It is also important that pharmaceutical companies understand their supply chains to determine what extent they are applying green chemistry methods and technologies.³

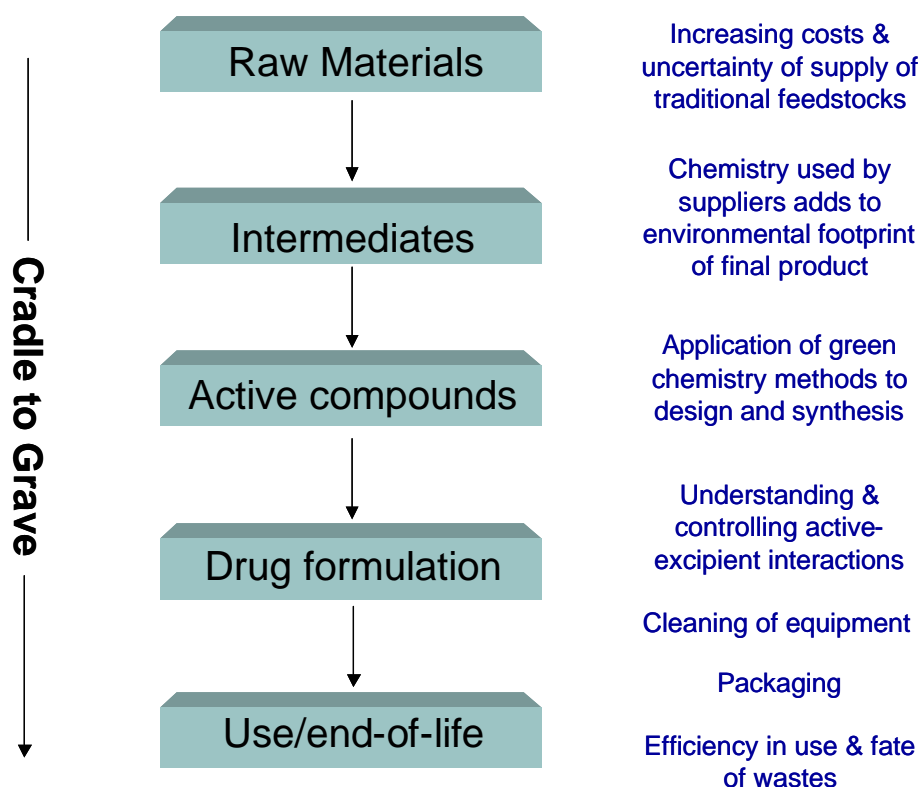
Key Issues and Discussion Points

- **How can the uptake of benign-by-design clean synthesis methods and green production technology within the pharmaceutical industry be increased? What incentives could be provided?**
- **Renewable resources are relatively unexploited within the pharmaceutical industry. With increasing cost and reduced availability of traditional feedstocks in future, could this be a valuable opportunity for further greening of PP manufacture?**
- **To fully exploit green chemistry opportunities, all areas of the business must have a common goal and work together.**
- **To ensure a process is truly green, companies must ensure they have a good understanding of their supply chains.**
- **Is increased out-sourcing of manufacturing steps by the major research pharmaceutical companies to often smaller companies located in other regions (where for example, legislation may be less strictly enforced) in conflict with a drive towards greener PPs?**
- **How can we persuade discovery and medicinal chemists to consider green chemistry in their work in addition to process chemists?**

4. Assessing Sustainability Implications of Pharmaceutical Products

When assessing the sustainability implications of both new and existing PPs, it is important to take into account each stage in their lifecycle. Figure 4.1 gives examples of considerations at different stages in the life cycle of drug manufacturing with respect to improving overall sustainability.

Fig. 4.1: Stages in Pharmaceutical Manufacturing



4.1 Life Cycle Assessment (LCA)

Life Cycle Assessment (LCA) is an environmental management tool used to examine, identify and evaluate the environmental implications of a material, process, product or system from creation to end-of-life, encompassing extraction and processing of raw materials, manufacturing, transportation and distribution, use and final disposal.⁵⁷ LCA determines inputs and outputs at each stage of the lifecycle, and aims to provide recommendations of how environmental improvements can be made. Clear system boundaries must be defined consistent with the aims of the study.

4.2 LCA of PPs

The application of full cradle-to-grave LCA for pharmaceutical products is not widespread. This is perhaps not unexpected; as for any type of chemical product full LCA of PPs is complex and time consuming. To carry out LCA on a chemical synthetic route or process, life cycle data must be obtained for all materials used in that process. This may be particularly difficult in the case of materials of interest to the pharmaceutical industry.⁵⁸ Pharmaceutical companies may also be reluctant to publish this type of information in the public domain, and may carry out these studies for internal documentation only. Only a limited number of examples of life cycle assessment of PPs were found in the literature.

C. Jiménez-Gonzales carried out LCA to evaluate, compare and select alternative synthetic routes and production processes to Sertraline Hydrochloride⁵⁹, an antidepressant manufactured by Pfizer, for her PhD research at NCSU. The scope of this study was cradle-to-gate i.e. it focussed on the overall environmental impact from the extraction of raw materials to the end of the manufacturing process and did not encompass use and fate. This methodology can therefore not be used to directly compare the full lifecycle implications of different PPs. The main findings of the study were:

- The two factors that have the most influence on environmental performance are solvent and energy usage;
- There is a strong link between the complexity of the system and the environmental aspects in the early stages of synthesis of a PP;
- A greater understanding of the relationship between the lab, pilot and full-scale synthesis can assist in the prediction of environmental burdens when selecting or designing a route.

The modular gate-to-gate methodology developed during this study is applicable to other PPs and was used by GlaxoSmithKline to assess the environmental impacts of a typical active pharmaceutical ingredient, providing consistent results. The development of the case study also provided GSK with ‘a well-documented life cycle methodology that may be used for strategic decision making, business processes and other processes and tools’.⁶⁰

Another study was carried out by D. Fichana at Rowan University on gate-to-gate LCA for pharmaceutical products with the support of Bristol Myers Squibb, which investigated four different lab-scale routes to Pravastatin, a drug used for lowering cholesterol.⁶¹ The study was

undertaken to determine how the environmental profile of the PP was affected by process improvements, and again use and fate were beyond the scope of the study.

GlaxoSmithKline have pioneered a so-called 'Fast Life Cycle Assessment of Synthetic Chemistry (FLASC™) Tool, which provides a way to both measure and benchmark the relative sustainability of the synthetic processes to a API (Active Pharmaceutical Ingredient).⁵⁸ The tool is based upon an in-depth assessment of the life cycle (cradle-to gate) impacts of the manufacture of materials commonly used in pharmaceutical processes and uses the methodology developed by C. Jiménez-Gonzales et al described above.⁶⁰ This web-based tool is particularly useful during the R&D stage of drug development, when routes and processes are selected and typically before Environmental, Health and Safety data are available. For each route or process examined, the tool provides:

- An overall life cycle environmental impact score, and a breakdown for all impact categories;
- A summary of the materials that have the greatest impact;
- Information on reaction mass efficiency, mass productivity and solvent acceptability;
- Appropriate guidance to allow improvements to be made.

This allows the user to evaluate and compare new synthetic routes, benchmark against existing processes and identify areas that would have the greatest influence on improving the environmental profile when developing future routes.

Again using the methodology developed by C. Jiménez-Gonzales et al described above⁶⁰, GSK have also applied life cycle assessment to expand their solvent selection guide⁵², which allows almost 50 different solvents to be ranked in terms of their potential impact across the lifecycle. In previous LCA studies on PPs⁵⁹, solvents were demonstrated to have a major influence overall on environmental performance.

The use of full LCA to make direct comparisons of the sustainability implications of pharmaceutical products from different companies is not feasible, as the parameters used and system boundaries set are subjective and are not standardised. From a review of the literature it also appears that of the limited studies available, none of these incorporate the use and fate stages in the life cycle of the PPs.

4.3 Cost Benefit Analysis

Cost-Benefit Analysis (CBA) can be used to estimate the value of the benefits and costs of implementing approaches to minimise the environmental impacts of PPs to pharmaceutical companies to establish whether they are worthwhile. Shifting the CBA in favour of the pharmaceutical companies may be a key factor in furthering the implementation of approaches by pharmaceutical companies to minimise the impacts of pharmaceutical products throughout their lifecycle.⁶² Constable et al. of GlaxoSmithKline report that ‘until society forces markets to focus greater attention on, and build standardised, accepted economic models for life cycle costs, it will remain difficult to assess these costs and make acceptable business decisions based upon these costs’.⁴³ In a collaborative programme with the American Institute of Chemical Engineers’ Centre for Waste Reduction Technologies (AIChE/CWRT), GlaxoSmithKline have been involved in developing a Total Cost Assessment (TCA) programme, which allows a monetary value to be attributed to life cycle impacts.⁶³

4.4 Green Metrics

There is a need to be able to clearly quantify the advantages of benign-by-design synthesis methods and green technologies (highlighted in section 3), to facilitate benchmarking between existing or proposed processes and to assist in decision-making. Metrics can provide a way to incorporate environmental data into cost and process factors in order to compare routes to different compounds.²⁷ They can also be used to predict and assess environmental issues. Typically process metrics do not include feedstocks or product fate, although it is important that they are applied with defined system boundaries, as with LCA. A number of green metrics have been reported that can be applied to measure the efficiency of a process/synthetic route including:

- **Atom Economy** - a measure of the number of atoms from the starting material that end up in the final product (introduced by Barry Trost).⁶⁴
- **Environmental factor or E-factor** - a measure of the amount of waste produced per kg of product (introduced by Roger Sheldon).⁶⁵
- **Effective mass yield** - the % of the mass of final product relative to the mass of all the other non-benign materials used in the process (introduced by Hudlicky et al.).⁶⁶ The incorporation of toxicity is an important aspect of this particular metric, although the

definition of non-benign can be open to interpretation and relies on the availability of human toxicity and ecotoxicity data.⁴³

- **Mass intensity** - the ratio of the total mass used in a process or process step and the mass of the final product. Total mass takes into account everything that is used in the process or process step except for water.⁶⁶ This may also be expressed as Mass productivity, the reciprocal of mass intensity expressed as a percentage.⁴³
- **Environmental quotient (EQ)** - similar to the E-factor above, but the result is multiplied by an environmental hazard quotient Q that takes into account the toxicity of the materials.⁶⁷

GlaxoSmithKline have published green chemistry measures for process research and development⁶⁸ and have developed other metrics in-house that are related to atom economy: reaction mass efficiency (RME) and carbon efficiency (CE).^{43, 63} RME is a more comprehensive method of assessing greenness as it incorporates the effect of yield and reagent excess, which is not the case when measuring atom economy, although solvent usage is still not included. CE measures the amount of carbon in the reactants that are incorporated in the final product, although this follows the same trend as RME and therefore does not provide any additional indication of how the greenness of a process can be improved.

In the development of an environmentally benign synthesis of sildenafil citrate³² Pfizer employed a range of green chemistry metrics including atom economy, reaction mass efficiency and E-factor to measure the improvements made at different time points throughout the process. DSM Pharmaceuticals and Hoffmann-La Roche have also published a comparative analysis of the syntheses of a key intermediate for the production of a leukotriene antagonist* using green chemistry metrics to quantify the potential environmental impacts of the different routes.⁶⁹

Metrics in common use are essentially chemical resource based and take little if any consideration of energy usage, despite the conclusions of Jiménez-Gonzales' studies. This is in part because allocation of energy to particular processes can be difficult when power consumption will be across an entire, multiprocess site. The principle of exergy analysis is that energy and materials consumption need to be considered together, a concept given added value when it is realised that in an organic chemicals intense operation such as the pharmaceuticals industry, the same raw material (petroleum) fulfils both functions (energy and materials). The first use of exergy analysis in pharmaceuticals was by Dewulf et al in

* Leukotriene antagonists are commonly used to treat asthma

2007, who used the approach to compare a chromatographic approach to crystallisation as methods for separating two isomers of an important pharmaceutical intermediate.⁷⁰ As with all in depth environmental impact analyses, detailed data inventories are required and these are rarely available for energy resource intakes. Nonetheless, the authors were able to demonstrate the methodology in a particular and real case, and to show that the exergy approach can lead to a counter-intuitive answer (in this case, the chromatographic method being less efficient). It also enabled resource efficiency ‘hot spots’ to be identified, typically loss of chemicals currently considered as waste, and the dissipation of energy to the environment.

4.4 Selection of Green Technologies

In addition to metrics that compare synthetic methods, GlaxoSmithKline have published guidance for the pharmaceutical industry on selecting the ‘greenest’ technology.⁷¹ This guidance aims to provide scientists and engineers with the necessary tools to make comparisons between available technologies used in the pharmaceutical industry from an environmental and safety perspective. It allows comparisons to be made between traditional and emerging technologies adopting lifecycle considerations and uses batch, mini and micro-reactors as a case study. This was further developed to allow technologies to be ranked in terms of environment, safety, efficiency and energy with the intention of incorporating a further consideration of economics in future.⁷²

4.5 Summary

Although the application of full Life Cycle Assessment of pharmaceutical products is unlikely to become a widespread means of measuring their sustainability impacts, it is essential that qualitative consideration of the lifecycle be made when carrying out any assessment. Tools such as FLASC™ developed by GlaxoSmithKline provide a good example of how we can begin to incorporate life-cycle thinking when measuring the ‘greenness’ of processes. Metrics also provide a useful method in assessing and comparing different synthetic routes to new and existing drugs and can highlight environmental issues at an earlier stage, although these should not be used in isolation. As mentioned previously, to gain a true assessment of the ‘greenness’ of a process, better understanding and control of the chemical processes of suppliers is needed

All of the methods found in the literature for assessing sustainability impacts of PPs do not include product fate - more attention should be paid in terms of measuring environmental impact such as biodegradability and environmental persistence. Measuring sustainability impacts of pharmaceutical processes and products is voluntary and is therefore down to the individual company to decide whether they wish to adopt such practices. Without industry-wide standards for 'measuring greenness' and methods for assessing the environmental issues beyond cradle-to-gate as previously reported, it will be impossible to make direct comparisons of the sustainability impacts between different PPs.

Key Issues and Discussion Points

- **Numerous methods exist to quantify the greenness of synthetic processes. However there is no standardisation for these methods as it is a voluntary exercise and hence is not possible to use these measures to facilitate benchmarking between products and processes from different companies.**
- **Consideration of energy requirements needs to be incorporated into process metrics.**
- **To obtain a true estimate of the sustainability implications of a PP, it is essential that 'use' and 'fate' issues are incorporated into any assessment.**
- **What could be done to introduce industry-wide standards for assessing the sustainability implications of PPs?**
- **Can metrics be effectively applied to outsourced processes?**

5. Towards Greener Drugs

5.1 Existing 'Greener' Drugs

Since the greening of Ibuprofen synthesis in 1992 by BHC Company, there has been a steadily increasing drive within the pharmaceutical industry towards the synthesis of 'greener' PPs. This is highlighted through the US Environmental Protection Agency's prestigious Presidential Green Chemistry Challenges Awards, which annually receive entries from pharmaceutical companies on the successful adoption of benign-by-design clean synthesis methods and green technology to produce PPs.⁷³ Table 5.1 overleaf highlights some of the most widely publicised improvements in the environmental impact of pharmaceutical product synthesis. These range from novel green catalytic methods, to reductions in solvent use, waste minimisation and elimination of hazardous reagents. The majority of these improvements were made after the drug was already on the market, providing an opportunity to address these issues at an earlier stage in the lifecycle. Until recently improvements to the processing of pharmaceutical ingredients was not permitted after the new drug application (NDA) had been filed with the FDA. This is a major step towards recognising the need to improve the environmental profile of drug manufacturing processes. The sooner environmental impact is considered during the development of PPs, the greater the chance of adopting prevention and minimisation techniques.⁷⁴

5.2 Improving the Eco-compatibility of PPs

As highlighted in section 5.1, the pharmaceutical industry has recently achieved numerous successes in greening its synthetic processes (gate to gate approach). However, little consideration has, so far, been given to the environmental impact of pharmaceuticals once they have left the industry (gate to grave approach).⁷⁵ In fact, most drugs are not fully metabolised in the body of animals or humans and are subsequently introduced into the environment. Their presence in the environment has led to growing concern from some parties. It is therefore crucial that we develop strategies to prevent pollution and limit the potential harm of pharmaceuticals on the environment. Such strategies could include:

i. Reducing burden of PPs at source: This can be done by reducing the amount of product ending up in the environment after use. Drugs should therefore be designed to minimise therapeutic doses. This approach is already employed by the pharmaceutical industry, which

is dedicating lots of time and effort to produce enantiomerically pure drugs (see section 3.1).⁷⁶ This method present the added benefit of eliminating exposure to the non-therapeutic isomers, which are often responsible for unwanted side effects. However, more research is required to improve the economics of racemic separation.

ii. End-of-pipe technologies: Most pharmaceuticals that originate from human and animal excretion are collected by wastewater treatment plants. A number of promising end-of-pipe technologies (including biological treatment and ozonation), which will allow efficient treatment of these micropollutants, are under development.⁷⁷ However, it is recognised that large parts of these products will always be lost to the environment.⁷⁴

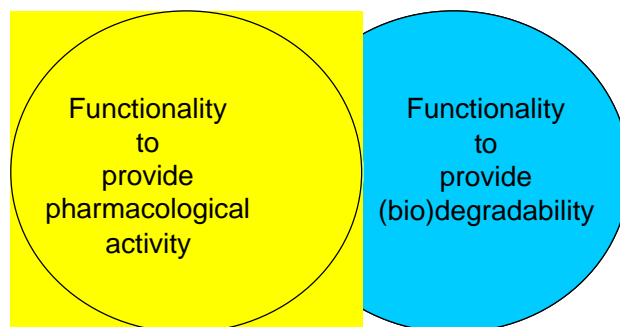
iii. Benign by design or design for biodegradability – Pharmaceutical products should be designed so that at the end of their function they break down into innocuous products and do not persist in the environment.⁷⁸ In fact, an environmental evaluation of a drug could potentially take place as an integrated part of the already long list of examinations required for approval of a new drug.^{79, 78}

There is broad knowledge that both therapeutic properties and biodegradability of PPs can (independently) be improved by systematic variation of chemical structure.⁸⁰ This approach, however, is very ambitious since active pharmaceutical ingredients rely upon their precise chemical structure to exhibit the desired biological activity and must demonstrate adequate stability and acceptable shelf life.³ The challenge for the pharmaceutical industry over the next decades will be, as highlighted by Kümmerer, to design new greener drugs in such a way that their lifetime is sufficient for their use but short enough under environmental conditions (i.e. a suitable balance between stability and biodegradability).⁷⁹ Nevertheless, it is important to note that, since the potential for degradation of pharmaceuticals greatly varies across their life cycle (i.e. different pH, temperature, redox conditions, bacteria and enzymes present, etc), stability during the application phase and degradability thereafter are not necessarily mutually exclusive (see Figure 5.1).⁸⁰

To the best of our knowledge, very little work has been done, so far, on the development of pharmaceuticals with improved biodegradability (benign by design strategy). Only two publications related to this subject could be found in the literature. Lee and co-workers introduced in 2000 the concept of a built-in chemical switch that once activated would lead to Fig. 5.1. Benign by design or design for biodegradability

Benign by Drug Design

- incorporating (bio)degradability into APIs



rapid decomposition and reported a new type of β -lactam antibiotic presenting in its structure a functionality that unmask over several hours of exposure to light.⁸¹ This light-induced unmasking generates a reactive functionality, which destroys the β -lactam moiety and hence eliminates its antibiotic properties.

Kümmerer also demonstrated that changing the chemical structure of an anti-tumour drug could dramatically enhance biodegradability with no negative effects on therapeutic activity.⁸²

In the meantime, a number of computer-based programmes have been developed over the last few decades to predict the biodegradability of chemicals (including pharmaceutical products) in the environment.^{83,84} These can be summarised under the generic term Quantitative Structure Activity Relationship (QSAR). The aim is to use descriptors that influence biodegradability and describe the chemical and physical properties of a new substance.⁷⁹ In principle, this method may avoid both expensive and time-consuming field degradation and animal tests as well as complex chemical syntheses.⁸⁰ However, predicting biodegradation pathways using QSAR systems is, and will probably remain, and inexact science, since it does not allow biodegradability to be predicted under real conditions.⁷⁹ Still, this can provide a convenient way for the pharmaceutical industry to quickly compare alternatives during both research and development.⁹³

Table 5.1: Examples of ‘greener’ drugs

Drug name/active ingredient	Company	Indication	Improvement	Stage in lifecycle of PP
Januvia™ (Sitagliptin)	Merck & Co., Inc	Type 2 Diabetes	Developed a novel catalytic method for asymmetric hydrogenation. The new route has fewer steps and >50% increase in yield, providing a significant reduction in raw materials, processing time, waste and energy. Strategy is broadly applicable to other pharmaceutical syntheses. ⁸⁵	New process developed after clinical trials
Lipitor® (Atorvastatin)	Codexis, Inc	High cholesterol	Greener reaction conditions developed which employ the directed evolution of three biocatalysts to produce the key chiral building blocks for the active ingredient in Pfizer's Lipitor®. Resulted in increased yield, improved worker safety, reduced waste and use of solvents, avoids use of hydrogen gas and reduces the use of purification equipment. ⁸⁶	?
Celebrex® (Celecoxib)	Pfizer Global R&D	Arthritis	Eliminated need for final recrystallisation step in manufacturing process – final isolation made direct from reaction mixture. Process efficiency increased in terms of raw materials, solvents, energy and waste ⁸⁷	New process approved after drug was already on the market
Lyrica® (Pregabalin)	Pfizer Global R&D	Neuropathic pain	Adoption of biocatalytic route, which eliminates need for organic solvents. Also allows undesired enantiomer to be recycled (previously could not be resulting in vast quantities of waste). ⁸³	New process approved shortly after drug was placed on the market
Irbesartan® (Avapro)	Bristol-Myers Squibb Company	Hypertension & Renal disease	Modification of synthesis to avoid production of non-biodegradable by-product requiring disposal by incineration. Reduction in use of hazardous materials, improved worker safety and energy savings through solvent recycling. ⁸⁴	New process developed after clinical trials
Emend® (Aprepitant)	Merck & Co, Inc	Chemotherapy induced emesis	New shorter and more efficient synthesis, which uses milder reaction conditions, doubles overall yield and reduces use of raw materials by 80%. ⁸⁸	New process approved shortly after drug was placed on the market

Zoloft® (Sertraline)	Pfizer Global R&D	Depression	Manufacturing process streamlined from 3 steps to one, using a more selective catalyst and more benign solvent. This achieved improved safety, reduced consumption of resources (energy and raw materials) and doubled the overall product yield. ⁸⁹	Improved commercial manufacturing process
Radafaxine	GlaxoSmithKline	Depression	Discovery and development of a green process for separating the two enantiomers of Radafaxine. Produces the desired enantiomer without expensive and environmentally unacceptable chiral catalysts or templates. It also replaces the environmentally undesirable solvents, allows recycling of the undesired enantiomer and significantly reduces waste. ⁹⁰	?
Accupril™ (Quinapril hydrochloride)	Pfizer Global R&D	Hypertension and heart failure	The redesigned process reduces raw material, water, and energy use significantly. It also has improved yields and a reduced number of steps. The new process avoids the use of a problematic solvent and solvent waste as a whole was reduced by 90%. ⁸⁷	?
Cymbalta®, (Duloxetine) & Strattera® (Atomoxetine)	Eli Lilly & Company	Depression & ADHD	An improved synthetic route avoiding the use of traditional N-methyl protecting group, which reduces the combined environmental footprint by an average of 44%, as measured by the weight of materials used to produce one kilogram of product (E-factor). ⁸⁶	?
Taxol® (Paclitaxel)	Bristol-Myers Squibb Company	Cancer	Green synthesis via plant cell fermentation and extraction. Replaces previous complex semi-synthetic method, requires no chemical transformations eliminating six intermediates and vastly reduces the amount of solvent, energy and chemicals required. ⁹¹	New process approved after drug was already on the market
Cytovene® (Ganciclovir)	Roche Colorado Corporation	Viral disease	More efficient process developed which halves the number of synthetic steps, reduces the number of hazardous waste streams and recycles/reuses a number of ingredients not incorporated in the final product. ⁹²	New process approved after drug was already on the market
LY300164	Lilly Research Laboratories	CNS disorders	New synthetic pathway using a biocatalyst and greener oxidation method. Fewer and inherently safer process steps, elimination of hazardous chemical and waste (chromium oxide & chromium waste), and reduction in use of solvent. ⁹³	Compound in early stages of development
Ibuprofen	BHC Company	Pain - inflammatory	New manufacturing process using three catalytic steps vs. old route of six stoichiometric steps. Virtually all starting materials are either converted to product or reclaimed by-product, or are recovered or recycled in the process, virtually eliminating all waste. ⁹⁴	New process approved after drug was already on the market

Finally, although recent interest in pharmaceuticals in the environment focuses on the active ingredient, consideration should also be given to packaging and excipients, which are inherent components of pharmaceutical products. Packaging size and package materials could indeed be improved to minimise waste (e.g. drugs passing their expiration date before use and use of non reusable or non recyclable packaging materials) and thus reduce the impact of PPs on the environment.⁷⁶ Similarly, it would be important to assess the environmental profile of some of the excipients, including preservatives and surfactants, which may exhibit significant biological activity.

5.4. Summary

Much effort has been done by the pharmaceutical industry to 'green' its manufacturing processes. However, little consideration has, so far, been given to the environmental impact of PPs at end of life. Strategies should therefore be developed to limit the potential harm of pharmaceuticals on the environment. Such strategies could include: (a) design of drugs with lower therapeutic doses; (b) development of more efficient wastewater treatment technologies; and (c) design of drugs that are benign by design or designed for biodegradability, i.e. break down into innocuous products at their end of their function and do not persist in the environment.

Key Issues and Discussion Points

- **Much work has been done to improve the sustainability of manufacturing methods; more focus is needed on environmental compatibility and end-of-life issues.**
- **Could eco-compatibility criteria for the design of greener drugs be proposed? As designing effective drugs that are successful in reaching the market is an extremely complex process, this may be perceived as yet another hurdle to overcome by pharmaceutical companies.**
- **If so, could this be a way of increasing the value of PPs that meet the eco-compatibility criteria in competition with cheaper, typically generic products?**

6. Classification and Labelling Schemes for Pharmaceuticals

Of the multiple possible approaches that can contribute to reducing the presence of pharmaceuticals in the environment, source control is seen as having the capacity of delivering important results. Source control includes targeting “hot spots” such as hospitals and nursing homes, but also actively influencing consumption volume and compound choice.⁹⁵ Particularly compound choice, i.e. opting for the environmentally friendly choice in case of alternative compounds being available with comparable effectiveness, can be addressed through *classification and labelling schemes*.

The following section 6.1 illustrates the most comprehensive existing classification and labelling scheme of pharmaceuticals, running in Sweden. This scheme targets specific active pharmaceutical substances and was first initiated by the Stockholm County Council and Apoteket (National Corporation of Swedish Pharmacies). The scheme is voluntary (the Swedish Medical Products Agency concluded in 2003 that, due to European rules, it was not possible to implement a mandatory classification and labelling scheme in Sweden.⁹⁶ In this scheme, information on the environmental impacts of pharmaceutical substances is made public on websites and information booklets but not via labels on drug packaging.

Section 6.2 briefly discusses the so-called eco-labels. Ecolabels also function on a voluntary basis but they are product-specific and appear on product packaging. Considerations for introducing ecolabels for pharmaceutical products remain so far on the theoretical level.

6.1 The Swedish classification and labelling scheme

6.1.1 The “Stockholm model”

The first approach implemented in Sweden was the one developed in cooperation between the Stockholm County Council and Apoteket in 2003; it is known as the “Stockholm model”. Its focus is on the environmental *hazard* of a pharmaceutical product, i.e. on its inherent ability to affect the environment. Due to the lack of official standards, a working model was developed, based on biodegradability (i.e. related to *persistence* in the environment), potential for *bioaccumulation*, and *toxicity* to aquatic organisms (called “PBT assessment”). The evaluation is based on data provided by the manufacturers. Every year, the evaluation of new active substances is made public (around 50 substances were added to the list in 2007).

The outcome of the classification is presented to the pharmaceutical expert groups of the Stockholm County Council. These experts use this information, as well as considerations regarding therapeutic efficiency, side effects, price, etc., in selecting the drugs that are recommended for use in the County Council health care. According to the Stockholm County Council, doctors displayed a high obedience (around 75%) to the recommendations of these pharmaceutical expert groups. The presumed achievements of the model were that doctors, health care staff and patients increase their awareness of possible environmental impacts of pharmaceuticals, and that the industry increases its efforts to design new biodegradable and not bioaccumulating drugs.⁹⁷

6.1.2 The “Swedish model”

In 2005, a complementary approach (“Swedish model”) was developed at the initiative of the Swedish Association of Pharmacy Industries (LIF), and in collaboration with the Swedish Medical Products Agency, Apoteket, the Swedish Association of Local Authorities and Regions, and Stockholm County Council. In fact, LIF and member companies were not very happy with the layout of the initial Stockholm model. For example, the level of metabolism in any given substance was not taken into account, so the amounts of the original substance that eventually reached the water supply would have been misleading.⁹⁶

There are two major differences between the Swedish and the original Stockholm model:

- (i) First, the evaluation of active substances are now not only based on the environmental hazard of the product, but an evaluation of both the hazard and the associated risk, i.e. an assessment of the *probability* that adverse effects will occur and of their possible extent, based on the current use of the pharmaceutical product.^{98,99} The environmental risk assessment is carried out by the Swedish Association of the Pharmaceutical Industry⁹⁹; it is based on the EU guidelines for environmental risk assessment of pharmaceuticals. The ambition of LIF is to have an environmental classification published on all substances available on the Swedish market within 5 years from the system launch in October 2005.⁹⁶
- (ii) Second, the information on risk/hazard is presented differently for three target groups with different levels of expertise: patients, prescribers, and specialists (scientists, experts, etc.) (see Annex I). The warning labels are not placed on the packaging due to European restrictions on the information that can be added to packaging of medication. The relevant information/labels are placed on websites; Stockholm

County Council provides both a detailed book on the subject background, and booklets with the latest classifications.

The possibilities of the Swedish model for limiting the discharge of pharmaceuticals into environmental waters seem considerable, particularly when considering the high compliance with expert groups' recommendations, the informing of both doctors and patients on the environmental aspects of their prescription practices, and the general awareness-raising regarding this issue.

In this context, it should be noted that the healthcare system in Sweden is highly particular, which has incidence on this Swedish scheme. All pharmacies in Sweden belong to the national retail monopoly Apoteket. Additionally, the Swedish health system is very public, with County Councils providing the health care for its inhabitants. The decisions of these institutions have great influence, both on patients and practitioners, which need not be the case in other national healthcare systems that are not as centralised. In addition, the issue of pharmaceuticals in the environment was taken up as one of the main environmental issues by both Stockholm County Council and Apoteket, and County Councils also write tenders for pharmaceuticals: including environmental criteria in these tenders is a possibility for the future.⁹⁷

All these points seem to have posed a significant incentive for the industry to participate in an environmental classification scheme of pharmaceuticals. In spite of the approach being voluntary, it seems to be the significant clout of the Apoteket and the County Councils, and the price of not participating in the scheme (i.e. not being able to influence the process), that created the incentive for industry to participate in it.

The initiative has overall allowed the industry to be regarded as a serious and collaborative partner by the stakeholders in environmental discussions. The industry has gained trust because of the transparency and openness of their knowledge and in some cases lack of data and knowledge. It is also likely that the model may spread to other countries. Mattson et al.⁹⁶ point out three things worth considering before implementing the system abroad:

- (i) Several developments and refinements to the model are ongoing (e.g., regarding the classification on persistence) and will not be fully implemented until after fall 2006.

- (ii) The availability of a specific internet portal (www.fass.se) for the information and classification has been critical for the launch in Sweden. Other countries must identify their most appropriate communication channel before their implementation.
- (iii) The PEC values have to be recalculated to fit the specific market in which the model is implemented.

6.2 Ecolabels for pharmaceuticals

Ecolabels are important instruments in an environmental policy mix. Compared to command and control mechanisms, they are more flexible and their introduction is easier, if supported by stakeholders.¹⁰⁰

To our knowledge, there are no ecolabels of the classical kind that address the issue of pharmaceutical products in the environment. Some proposals have only been made so far to address the related personal care products (e.g. cosmetics, sun-screen products). The regulation of personal care products is in many respects less stringent than that for pharmaceuticals.

Contrary to the classification and labelling approach implemented in Sweden, which targets individual active substances, ecolabels target products and the labelling information should appear on product packaging. Active substances can be part of various pharmaceutical products. It is often the case that chemicals of very different origin and purpose (e.g. active substance and other chemical compounds necessary for stabilising the intake of the drug) are mixed in a product, and as a consequence released jointly into the environment. By addressing the product as a whole, an ecolabel could be a step towards more sustainable chemistry in pharmaceuticals; this is often termed “green pharmacy”.¹⁰¹

A possible drawback of ecolabels is that voluntary participation is limited to reaching only part of the manufacturers. Additionally, ecolabels appeal to a limited part of market consumers. Especially, in the case of pharmaceuticals, market consumers choose themselves only over-the-counter drugs but not drugs prescribed by the doctor. Experience with ecolabels in other sectors shows that there is a possibility of a larger number of consumers participating, if labelled products are priced competitively regarding non-labelled ones. In the case of pharmaceuticals, however, price is not considered to be as influential on consumption as in other sectors (e.g. food).

Furthermore, the type of label most often discussed when referring to pharmaceutical products is that under the control of independent third parties (Type I environmental labelling programmes, ISO 1999). Such labels should be distinguished from labels that are set up by single companies (or, possibly, by industries) that serve as advertising and where the criteria for labelling are not public. Examples of well-known third-party ecolabels are those of the Forest Stewardship Council (FSC), Marine Stewardship Council (MSC), and the German “Blue Angel”. Voluntary approaches, not reviewed by third parties, can be deceptive, serving corporate interests instead of the public good.¹⁰² In addition, the issue of what information a label provides, and how it is communicated, is also of crucial importance.¹⁰²

All in all, however, ecolabels could be helpful in initiating public discussion on the topic of pharmaceutical products in the environment, particularly when linked to the issue of pharmaceuticals in drinking water.

Key Issues and Discussion Points

- **Key issues for developing and implementing classification & labelling schemes (including ecolabels) are which information is used as the basis for classification, the standardisation of the information being used, the criteria applied in the classification, who provides the information required and mode of communication.**
- **Is the Swedish classification and labelling scheme of interest for adaptation and implementation in other countries and how? Possible role of other national healthcare systems? Is the extension of a model along the lines of the Swedish one possible and desirable on the European level? Which additional characteristics would this model have to have?**
- **Except for the scheme applied in Sweden (targeting active pharmaceutical substances), there are no ecolabel schemes for pharmaceutical products in Europe yet.**

7 Drug take-back schemes

7.1 Introduction

The development and set up of take-back schemes of unused/expired medication is a quite widespread post-pharmacy stewardship approach for reducing the discharge of pharmaceutical products into waters.

In a recent survey of expert stakeholders' views (including government, academia, pharmaceutical and consulting industries)¹⁰³, the implementation of take-back schemes was put forward as the most popular risk management strategy for pharmaceuticals in the environment. In this context, take-back schemes were seen best coupled with public education. Although the contribution of improper pharmaceutical disposal to the environmental loading of pharmaceutical products is not well understood and is generally believed to be minor, one of the interviewed stakeholders explained that take-back schemes are seen as a positive management response because disposal of unused and expired medicine seems like a logical, easy portion to remove from the environmental loading.

In Europe, take-back schemes for unused or expired medicine are required since 2004 by EU legislation. Directive 2004/27/EC requires Member States to “ensure that appropriate collection systems are in place for human medicinal products that are unused or have expired” (Article 127b).¹⁰⁴ Reference to these collection systems is to be made on the labelling or package leaflet. These systems had to be set up by the end of October 2005. As concerns veterinary products, the requirement to have appropriate collection systems dates from 2001 and was set out by Directive 2001/182/EC.¹⁰⁵ The following focuses on take-back schemes for human medication.

7.2 National take-back schemes

According to the European Federation of Pharmaceutical Industries and Associations¹⁰⁶, 20 European countries (out of 28 countries surveyed) have a drug take-back scheme in place. Seven countries however have no scheme,^{*} and no information was available for Luxembourg. Eleven of the schemes in place are managed by pharmacies, six are co-ordinated nationally and five locally. The majority of the returned material is incinerated.

* Bulgaria, Cyprus, Greece, Latvia, Malta, Romania and Slovenia.

Quantitative information on the performance of the existing drug take-back schemes is not readily available for many countries. In fact, in the recent survey of 28 countries mentioned above, only ca. 30% of respondents were able to provide actual data. According to these responses, 19k tonnes of medicine have been recovered from 8 countries (figures may also include packaging).

The following gives some more detailed information on France and Sweden, which are considered to have the most comprehensive human drug take-back schemes operating at present. Annex II gives information also on schemes operating in Germany and the UK.

7.2.1 France

In 1992, France issued a decree specifying that all manufacturers of products for the general public had to contribute to the elimination of the waste resulting from the packaging of these products (Décret N° 92-377, 01.04.1992). The manufacturers could choose one of two forms for the organisation of the elimination: participation in a common system, *Éco-emballages*, or setting up their own system. The French pharmaceutical industry chose the latter option, setting up CYCLAMED in 1993. CYCLAMED originally had two main functions: It organised and financed the incineration of medicinal waste and packaging, and sorted unused medicine to distribute it to NGOs for reuse in Eastern Europe, the global South, or among people in France without social protection. Consumers were to bring their pharmaceutical wastes and packages to their chemist, who was in charge of collecting and sorting it.

Following press attention on cases of deceptive use and resale of unused medicine by certain chemists, the Minister for Health and Social Protection demanded in 2004 a review of the system. The resulting report¹⁰⁷ pointed out several weaknesses and problems in the system, among others the low rate of packaging and medicine collecting, the unsuitability of unused medicine for redistribution, especially in the global South, and the risk of fraud linked to the reuse of medicine.

A law was eventually passed in early 2007 stating that pharmacists were to collect, free of charge, unused medicine brought to them by the consumers (Loi n° 2007-248, Art. 32).¹⁰⁸ From the end of August 2008 and onwards, the redistribution and reuse of collected medicine will be forbidden. The medicine is to be destroyed “under secured conditions”.

CYCLAMED collects 5,7% of the medicine sold yearly. At the same time, Grass and Lalande¹⁰⁸ estimate that on average, one out of two prescribed medicine is not consumed (i.e. ca. 50% of medicine sold). Therefore, the collection rate of medicine sold but not consumed seems not to be very high. Having said that, there are different and contradicting estimations of the effectiveness of the French drug take-back scheme. For instance, Taylor & Poulmair¹⁰⁶ mention an estimated recovery rate of up to 80% for the take-back scheme of France.

7.2.2 Sweden

The Swedish take-back scheme is strongly determined by the structure of its healthcare system. All pharmacies in Sweden belong to the state-owned Apoteket (National Corporation of Swedish Pharmacies), which provides this company with significant powers in its dealing with other stakeholders.** Apoteket runs a pharmaceutical take-back scheme (since the 1990s), in which consumers can return their unused or expired medication to any of the chain's pharmacies. These pharmaceuticals are then collected and incinerated in approved incineration plants.

There is a high level of awareness of Apoteket's take-back scheme among the Swedish public. Apoteket claimed in 2004 that approximately 65% of the Swedish public disposed their unused medications by returning them at pharmacies, whereas in 2006 the figure had increased to 73%. In the year 2006, the amount of pharmaceuticals returned increased by 4% compared to the previous year.¹⁰⁹

The company has invested significant efforts in increasing the available information on the environmental risks of drugs,* and in increasing the public's awareness of the environmental consequences of their disposal. Among the latter are campaigns that address the public's behaviour regarding surplus or leftover drugs (e.g. through advertising in newspapers and poster distribution).

Other approaches used by Apoteket and others for reducing the environmental impact of pharmaceuticals include reducing the amount of unused medicine, e.g. through the use of "starter packs", which reduce the amount of leftover medicine in the case of treatment being interrupted.⁹⁹

** This retailing monopoly will be broken up and by January 2009 new companies should be permitted to enter the business, according to the promises of the recently elected government.

* See also section 6.1 on Sweden's classification and labelling schemes that inform the general public on environmental risks of pharmaceutical products.

Apoteket does not deliver numbers regarding the total amount or the percentage of dispensed medicines that are returned to pharmacies. Information derived from other studies seems to indicate that, in spite of 73% of the public claiming to return their medication, the proportion of unused medication that is returned may not be as large. According to studies cited in Ekedahl (2006),¹¹⁰ the proportion of dispensed medicines returned to pharmacies range between 2,3 and 4,6% of the total volume dispensed (studies published in 1999 and 2003). In the book “Environment and Pharmaceuticals”, published in collaboration between Apoteket, Stockholm County Council and Stockholm University, the proportion of drugs that never get used is placed at “about 5 per cent”.¹¹¹ This estimation may be optimistic, considering for example that for France, Grass and Lalande¹⁰⁶ estimated that on average one out of two prescribed medications is not consumed (i.e. ca. 50% of medicine sold).

Key Issues and Discussion Points

- **The extent of establishment and the degree of effectiveness of take-back schemes for human drugs is quite different among European countries.**
- **In-depth assessments of scheme effectiveness (estimated recovery rate of unused/expired drugs) are missing. Individual available assessments often quote different and contradicting figures, pointing to the need for a more consistent approach that should be used in such evaluations.**
- **High levels of public awareness and education on the environmental consequences of the disposal of unused/expired drugs are key for the success of such schemes.**

8. Approaches to Communicate Methods of “Good Practice”

8.1 Introduction

Eco-pharmacostewardship may be employed to reduce the environmental impact of pharmaceutical products throughout their life cycle. In the following section, approaches to communicate methods of “good practice” to manufacturers, prescribers and users of pharmaceuticals are examined. Environmental considerations regarding drugs should be emphasised in order to include them throughout the life cycle of a drug. Measures to reduce drugs’ potential effects on the environment must be based on current knowledge, particularly on acute and mainly long-term effects.

8.2 Informing the public

Strategies to enhance public awareness have to be developed in order to stimulate an environmental approach. Society wants and needs information and training regarding the effects of drugs on the environment.¹¹²

What type of information can be provided and how?

1) *When known, information on pharmaceutical substances effects on the environment could be provided through products résumés and pack inserts.*

The information concerns mainly chemical and biological data on pharmaceutical substances, their metabolites and excipients. This information has to be based on scientific data and not delivered in the form of an advertising message. The knowledge on existing environmental data has to be continually updated and needs to be turned into relevant and practical information. News on drugs and their effects on the environment should be presented in the same way as for news on side effects, interaction, on websites of relevant agencies. European legislation currently provides the opportunity for the product résumé to include information on veterinary drugs’ effect on the environment. Is there an equivalent facility for human drugs?

2) Information on source-based sorting of packs and handling of superfluous drugs and handling of used drugs that contain substance residues can be issued through product résumés and pack inserts

3) *Other resources*

Edit texts (brochures, posters) targeting the general public regarding return of superfluous drugs to pharmacies. Brochures, posters could provide directions on what is accepted and not accepted, how to return the unused or expired medications and where to go in easy fashion. These brochures could be made available in pharmacies; their distribution could be extended to municipalities, and could be inserted in local newspapers, bulletins of healthcare communities (doctors, vets etc). Information should be disseminated as largely as possible through relevant websites and networks.

Establish awareness campaigns (one week for example) inside chemists: for example the pharmacist could provide a brochure to everyone with a prescription, showing, through a simple scheme, the unwanted or out of date medicines route from the toilet/sink to the environment.

8.3 Involvement of producers and distributors

In a survey on the household disposal of unused and expired pharmaceuticals as a source of pharmaceutical compounds in the environment, it emerged that a prominent disposal route of out-of-date or unwanted medicines may be via the sink/toilet or in household waste.⁷⁷

In response to rising trends in prescription drug abuse and potential environmental concerns, the US Federal prescription disposal guidelines (2007) include flushing when it is instructed to do so and return of unused, unneeded or expired medicines to pharmaceutical take-back locations for safe disposal. Through pharmaceutical-return programs, residual medications can be collected from the public at take-back locations and disposed of in environmentally sound manner. In the same frame, the concept of “Extended Producer Responsibility” (EPR) for manufacturers and distributors has been implemented in British Columbia.¹¹³ Those who produce, use or sell a product are responsible for the impacts of the product throughout the stages of its life cycle, including the end of life, waste management stage. The regulation require all brand owners of pharmaceutical products sold in British Columbia to take responsibility for the management of their products by providing a way for the public to dispose of their unused or expired products in an environmentally responsible manner.

Key Issues and Discussion Points

- **It is important to ensure that information regarding pharmaceutical products in the environment is provided to manufacturers, prescribers and users. How can scientific knowledge be turned into relevant and practical information? Who can do this?**
- **Product résumés and pack inserts appear to be an interesting means of communication. Is there a need for a revision of guidelines for product résumés and pack inserts? Is there legal support for stating environment-related information on the drug packs themselves?**
- **Promoting “extended responsibility” within producers and distributors community is a key issue. At the European level, could EFPIA (European Federation of Pharmaceutical Industries Association) be a relevant body to promote this concept?**
- **A possible communication method could be the creation of an “eco-label” dedicated to “ecologic drugs”. What are the regulatory “resources” for this?**

8.4 Training

Universities could include environmental knowledge in courses for professional categories (doctors, pharmacists) involving prescription/handling of drugs. In the same way, information of the environmental effects of drugs could be introduced in environment related courses. The corresponding teaching aids (e.g. power points) could be made available on relevant websites of stakeholders (professional associations, environmental agencies, etc).

Awareness of secondary school students must be stimulated, too, as well as primary education: currently, it is observed that information about recycling, given at the primary school, influences the parents' behaviour and hence there is an opportunity to achieve this with environmental stewardship of pharmaceuticals.

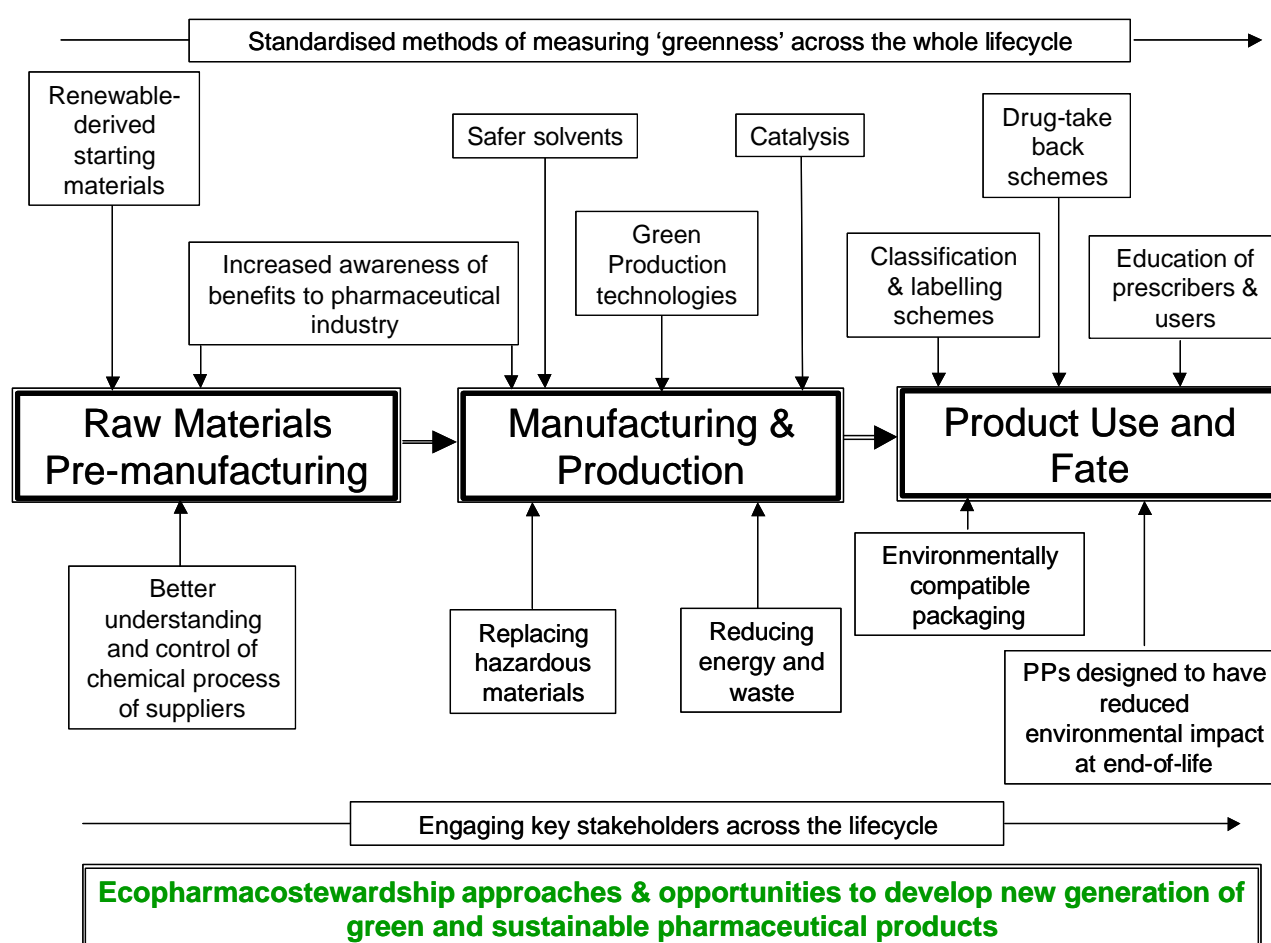
Key Issues and Discussion Points

- **Training has to be developed in order to improve public awareness and attitude regarding pharmaceuticals in the environment. Dissemination of knowledge has to be done at the different education levels.**
- **What types of educational materials according to the targeted public? Printed materials? Web sites? Advertisement on TV?**
- **What programs? How to evaluate effectiveness and performance of measures?**

9. Conclusion

The following diagram summaries the eco-pharmacostewardship approaches and opportunities that have been identified which could be applied to reduce the impact of PPs on the environment at all stages in the lifecycle. All of these factors should be taken into consideration when developing new PPs to ensure that they have as few adverse effects as possible whilst at the same time maximising their beneficial effects, leading to the development of a new generation of green and sustainable pharmaceutical products

Figure 9.1. Summary of the key findings of the discussion document



9.1 Development of Eco-compatibility Criteria

Drug design and formulation should factor in new considerations for “environmental friendliness”. Through KNAPPE, a number of eco-compatibility criteria have been identified to measure the overall environmental footprint of PPs (see Figure 9.2):

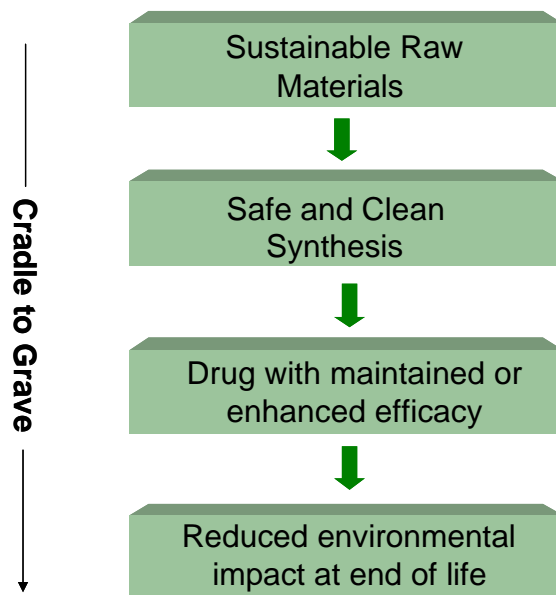
1. Derived from sustainable raw materials: most current drugs are derived from petroleum, which is a finite and non-renewable resource and is becoming an increasingly expensive raw material. In the long-term, new drugs should therefore be derived from biomass, which represent a renewable alternative to petroleum (see section 3.4). In the meantime, it is vital that the pharmaceutical industry gain a better understanding and control of the origin and sustainability of its raw materials and intermediates.

2. Safe and clean synthesis: new drugs should be designed using green chemistry and clean technology, minimising waste and maximising energy efficiency (see section 3.1-3.3). The pharmaceutical industry has already developed a number of tools to assess the environmental profile of their processes and has achieved numerous successes in greening its synthetic processes (see section 4.3 and 5.1).

3. Maintained or enhanced efficacy: it is of paramount importance that greener pharmaceuticals exhibit maintained or enhanced efficacy with limited side effects compared to any alternatives since they are extremely important to human health and, in many cases, can save lives!³

4. Reduced environmental impact at end of life: it is also crucial that we consider the environmental impact of drugs at the end of life as an important factor while developing a new pharmaceutical product. Future greener drugs will need to be designed to have the desired effect within the human body and take into consideration their effect on ecosystems after having passed through the human metabolic system (see section 5.2).⁷⁴ Considerations should also be given to packaging and excipients, which are inherent components of PPs. In parallel, more efficient take-back schemes for unused/expired PPs need to be established in order to minimise the discharge of pharmaceuticals into the environment.

Figure 9.2. Toward greener drugs: development of eco-compatibility criteria



Ultimately, the greenness of drugs could be ranked against the above criteria to allow comparison of pharmaceutical products from an environmental and sustainability point of view. In Sweden, for example, an environmental classification system for pharmaceuticals has recently been developed in cooperation with industry (see section 6.1.1). This labelling basically allows doctors and patients to take into account the environmental impact of drugs at the end of life (persistence, bioaccumulation and toxicity) when comparing medications for a particular treatment that are equally safe and effective. Thus providing the information required to select the treatment that is more environmentally friendly.¹¹⁴ In the light of the four eco-compatibility criteria identified through KNAPPE, a more comprehensive scheme, based on the labelling system developed by the Stockholm Country Council, could be envisaged for greener drugs incorporating additional information, across the life cycle, regarding raw materials as well as drug synthesis and formulation.

9.2 Key Recommendations for the Increased Development of Greener PPs

- The implementation of tax or other incentives to make benign-by-design clean synthesis methods, green production technology and other stewardship approaches more attractive. Encourage pharmaceutical companies to make increased use of renewable resources part of company longer-term (e.g. 5+ years) plan (possibly extending to renewable energy). This should be done alongside a campaign to increase awareness of the benefits of increased uptake of these methods (e.g. reduced costs in manufacturing through more efficient use of resources, avoidance of

hazardous chemicals, reduced number of process steps, etc) to the pharmaceutical industry, in particular amongst high-level managers to drive change within the business.

- Move towards standardisation of methods to quantify the sustainability implications of PPs to facilitate benchmarking between products and processes from different companies including consideration of all stages in the lifecycle of a PP and incorporating energy requirements. These should also be applied to pharmaceutical intermediate suppliers and companies to whom manufacturing steps are out-sourced to ensure greater understanding of supply chains.
- Development of eco-compatibility criteria to score PPs on their environmental impact at all stages of their development including post consumer fate to encourage the pharmaceutical industry to design greener drugs and provide much needed focus on environmental compatibility and end-of-life issues (see Section 9.1. above). This could provide a further incentive to pharmaceutical companies if it provided a competitive-edge to PPs that met these criteria over those that did not.
- Use of these eco-compatibility criteria to develop a classification and labelling scheme to provide relevant and practical information for prescribers and users of PPs. This could be based upon an expansion of the Swedish classification and labelling scheme and could be implemented in other countries (see Section 9.1. above).
- Lobby for users to give preference to greener drugs (e.g. hospitals/national and local authorities)
- Conduct a study into what would make ecolabels for pharmaceutical products effective and for which types of products in specific (e.g. over-the-counter vs. prescribed drugs). Eco-labels on product packaging for PPs represent a valuable communication method on the environmental impacts of PPs, although this would require a revision of guidelines and legal support.
- Raise public awareness of the issues surrounding the environmental impacts of PPs and the solutions provided by eco-pharmacostewardship approaches through engaging with NGOs and running promotional campaigns. Incorporate education and training of these issues into school and university curricula, as well as Continuing Professional Development for key stakeholders.
- Promote extended responsibility for PPs within producers and distributors. At a European level, EFPIA (European Federation of Pharmaceutical Industries Association) could potentially be a relevant body to promote this concept.

Annex I: Environmental risk information in the Stockholm model

The environmental risk assessment in the Stockholm model for classification and labelling of pharmaceutical substances is based on EU guidelines for environmental risk assessment of pharmaceuticals.* The information on risk/hazard is presented differently for three target groups with different levels of expertise: patients, prescribers, and specialists (scientists, experts etc.).

At the patient level, and based on the PEC/PNEC ratio outlined above, a verbal message is provided for the patient's information:

$PEC/PNEC < 0.1$ **“Use of the medicine has been considered to result in insignificant environmental risk.”**

$0.1 < PEC/PNEC < 1$ **“Use of the medicine has been considered to result in low environmental risk.”**

$1 < PEC/PNEC < 10$ **“Use of the medicine has been considered to result in moderate environmental risk.”**

$PEC/PNEC > 10$ **“Use of the medicine has been considered to result in high environmental risk.”**

If there is not sufficient data to calculate the PEC/PNEC, the following statement is used:

“Risk of environmental impact cannot be excluded due to lack of data.”

In the case where the $PEC:PNEC < 1$, but the medicine is considered as having potential PBT or vPvB (very Persistent, very Bioaccumulative), the risk phrase is replaced with the phrase:

“Hazardous environmental properties.”

At the prescriber level, the environmental risk information given to patients is repeated, but it also includes additional information on the environmental persistence (degradation) and bioaccumulation of the active substance.

Degradation: **“The medicine is degraded in the environment”, or “The medicine is slowly degraded in the environment”, or “The medicine is potentially persistent”.**

Bioaccumulation: **“No significant bioaccumulation potential”, or “Potential to bioaccumulate in aquatic organisms”.**

* The European evaluation of pharmaceuticals is based on a *risk* assessment, which combines an assessment of the hazard of a substance, with an assessment of the environment's exposure to it. The parameter that addresses the former is termed Predicted No-Effects Concentration (PNEC), and is a conservative estimation of a threshold concentration at which an active substance does not produce negative effects on aquatic biota, based on ecotoxicological tests. The environment's exposure to the hazard is addressed through the Predicted Environmental Concentration (PEC) of the compound, based on the population's water consumption and a realistic worst-case estimate of the pharmaceutical's use (i.e. high use), or on actual use data if available. The decision criteria are based on the ratio of both values.

If the pharmaceutical fulfills the criteria for PBT and/or vPvB, the following phrase is added:

“According to the established EU criteria, the compound should be regarded as a PBT/vPvB substance.”

If there is insufficient data to characterize the potential for degradation, the following statement is used:

“The potential for persistence cannot be excluded due to lack of data.”

If there is insufficient data to characterize the potential for bioaccumulation, the following statement will be used:

“The potential for bioaccumulation cannot be excluded due to lack of data”

At the specialist level, all environmental information available is provided. Some examples are ⁹⁸

- Risk assessment, i.e. PEC/PNEC, calculations as well as the specific PEC and PNEC calculation, given in microgram/l, where applicable.
- Total sold amount in kilograms of the active substance on the market (including all products and enantiomers containing the same active substance) in the most recent year for which data are available.
- Results from ecotoxicity tests (given in microgram/l).
- Test guidelines used (e.g. OECD, FDA).
- Information about which forms the pharmaceutical is excreted as, parent compound as well as metabolites, and the percentages thereof.
- Data interpretation in the context of risk and hazard assessment.

(The shortcomings involved in the information available and the methodology used are highlighted in Apoteket (2006)).⁹⁸

In addition to providing this information, Stockholm County Council gives prescribers a series of recommendations, such as to encourage patients to return their unused medications at pharmacies, inform patients of the importance of returning estrogen patches, prescribe starter packs, review and regularly reassess the patient's total consumption of medication in order to reduce waste, etc.

Annex II: Selected national drug take-back schemes

United Kingdom

In 2005, the UK passed a legislation amending the 1992 National Health Service Regulations (S.I. 2002/662) to govern the provision of pharmaceutical services. According to these regulations, “[a] pharmacist shall ... accept and dispose of unwanted drugs presented to him for disposal” (United Kingdom, 2005: Schedule 1, Part II, Art. 12)¹¹⁵. Pharmacies thus have to take back and sort unwanted and/or unused medicines brought by the patients. The collection is not financed nor organised by the pharmaceutical industry but by local health authorities. Returned medicines are incinerated.

According to a study by the National Health Service¹¹⁶ all of the Local Health Boards (LHBs, in Wales) and Primary Care Trusts (PCTs, in England) had a scheme in 2004-05 for the collection and disposal of unwanted medicines through pharmacies.¹¹⁶ The NHS collected detailed information on the weight of unused/ unwanted medicines taken back by 252 of the PCTs.¹¹⁶ However no information is available on the estimated relation between sold drugs, the rate of these drugs that are potentially unused, and the rate of unused drugs taken back to the pharmacy.

Germany

In Germany, old unused medicines are legally classified as residual waste and can be disposed of with regular waste. However, two companies operate drug take-back systems, Vfw-Remedica and MEDirecycling. Both collect unused medicines from pharmacists, sort and recycle the packaging and incinerate pharmaceuticals. Vfw-Remedica was founded in 1995 and covers about 16000 of the 21000 German pharmacists as well as 2000 hospitals and further health facilities.^{117,118} MEDirecycling dates from 1997 and takes the medicine back from only a few thousand pharmacists, as well as from hospitals and retirement homes (see www.medirecycling.de). As concerns the disposal of drugs by private consumers, Innovations Report (2002)¹¹⁹ mentions that 86% of the 1,6 billion medication packaging disposed yearly is documented in private households (and partly disposed via the Green Dot (Grüner Punkt) household recycling system). Only 14% is returned to the pharmacies. A survey showed that 95% of the respondents know the “Green Dot” sign for packaging recycling but only 3% are familiar with the Vfw-Remedica system for pharmaceutical products. Additionally, only few pharmacies offer easily accessible collecting boxes and relevant instruction signs are missing in 9 out of 10 cases.

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