

Green pharmacy practice

Taking responsibility for the environmental impact of medicines

2015



International
Pharmaceutical
Federation

Colophon

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Foreword

By the Co-chair of the FIP Working Group on Pharmaceuticals and the Environment

The International Pharmaceutical Federation (FIP), representing three million pharmacists and pharmaceutical scientists around the world, has discussed the environmental problems that pharmaceuticals can cause when not used or disposed of appropriately. FIP set as one of its priorities for 2013–2015 the development of practical tools on pharmaceuticals and the environment, to provide practising pharmacists with the necessary resources for taking environmental aspects into consideration in their daily professional activities.

For this purpose, in 2013, FIP appointed a joint Working Group on Pharmaceuticals and the Environment. Its charge was to develop a reference document that provides key information, and to provide pharmacists with references that document this important issue.

To obtain current national and regional information, the working group surveyed FIP member organisations about existing practices, legislation and frameworks.¹ This survey showed that there is a need for discussion, and to educate pharmacists on and strengthen their role in environmental issues.

Although much remains to be addressed on the subject of “green” pharmacy, FIP is committed to providing practising pharmacists with the necessary information and tools for incorporating sound environmental practices into consideration in their daily professional activities.

Eeva Teräsalmi

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Executive summary

This reference document, “Green pharmacy practice: Taking responsibility for the environmental impact of medicines” was prepared by a joint working group of the Board of Pharmacy Practice (BPP) and Board of Pharmaceutical Science (BPS) of FIP. The report is intended to inform FIP member organisations and individual members about the environmental issues that surround the medicines-use process.

The document presupposes that there is a level of responsibility for all stakeholders, including pharmacists, to change the entire medicines-use process so as to minimise the environmental effects of pharmaceuticals; this means prescribing, dispensing, pharmaceutical care and disposal of unused medicines, as well as waste discharge into the environment.

The document describes current findings on pharmaceuticals levels in the environment and the different ways that pharmaceuticals find their way into the water supply, soil and atmosphere. It describes some of the negative effects that active pharmaceutical ingredients (APIs) may have on living organisms, including hormonal or nervous-system effects on aquatic animals, which in severe cases could cause population collapse.

In the face of substantial research that documents both the cause and effect of pharmaceutical discharge into the environment, the report offers a wide array of solutions. It recognises that these include an awareness that results in positive actions by all those involved with medicines — from researchers, through manufacturers and sales people to providers and, ultimately, consumers.

Underlying the actions of citizens must be supportive public policy and law. The report provides a brief overview of some of the policy initiatives, and agency activities of multinational, national, regional and local governments and non-governmental organisations.

In proposing ways to address this issue there is an extensive discussion of market segments and ways in which each can have a positive impact. These segments include hospital and institutional practice, community and ambulatory practice, the pharmaceutical industry, wholesaling, office management, and the public. There is also a discussion of the value of interprofessional collaboration and the need to address the subject within professional education curricula.

This report provides many examples of current practices occurring in various parts of the world and is extensively referenced.

By accepting the professional challenge of reducing the environmental impact of the medicines for which pharmacists are responsible, the profession can provide meaningful leadership in an area where leadership is desperately needed.

1 Issues to be addressed

1.1 Pharmaceuticals in the environment

1.1.1 Incidence of pharmaceuticals in the environment

The development of new analytical technologies that can measure increasingly lower concentrations has seen an increased focus on the detection of the residuals of active pharmaceutical ingredients (APIs) — biologically active substances — that can be found in the environment. These substances can occur in the environment at concentrations of ng/L–µg/L.²

The German government has been conducting and funding studies in areas such as pharmaceutical contamination in soil and sludge through emissions from production processes, sewage and waste-water treatment plants. An extensive research project investigated a total of 123,761 incidents of measured environmental concentrations of pharmaceuticals around the world. The majority of these concentrations were found in sewage, waste-water treatment effluent and surface water. Traces of pharmaceuticals have been found in drinking water and even in mineral water.³ Only a few were found in soil, sediment and slurry.⁴

Altogether, 559 different pharmaceuticals or their metabolites have been found in waste-water treatment influent, effluent and sludge. Furthermore, 38 different pharmaceuticals were found in surface, ground and drinking waters. Large concentrations were found in Europe and North America. Among the 16 pharmaceuticals most frequently detected in surface, ground and drinking waters, most were in Europe — most prevalent were the analgesic diclofenac and the antiepileptic carbamazepine. For example, diclofenac was detected in 36 of 50 samples from Western Europe. The problem of pharmaceutical pollution may be even more extensive than currently recognised due to limitations of instrumental analytics, whose existing methods are applicable to only some of the pharmaceuticals out of the thousands that are manufactured.⁴

How much do we know about the environmental impact of pharmaceutical products? In several countries/regions, environmental data are part of the dossier submitted by a pharmaceutical company to pharmaceutical agencies in the registration process (i.e. when applying for market authorisation). One example is the environmental data requested in the Environmental Risk Assessment (ERA) required by the European Medicines Agency (EMA). These data include eco-toxicity, degradation and bioaccumulation. A series of standardised tests is used to assess the environmental impact of the medicine.

The potential environmental impacts throughout the life cycle of a medicine are not yet well known to the different stakeholders within the health care sector (e.g. raw material suppliers, pharmaceutical manufacturing companies, marketing and sales organisations, pharmacies, patients, payers and regulators).

In order to be able to understand the environmental challenges the industry and other parts of the health care sector are facing, it is important to understand issues such as the potential conflict between rapid biodegradability and medical effect. To minimise environmental impact, substances should be easily biodegradable; this would enable removal of the substance from wastewater in a sewage plant. However, the chemical characteristics that make a substance biodegradable in the environment may also limit its half-life in the body and therefore reduce its therapeutic benefit. A similar potential conflict exists between medical effect and minimal environmental impact when it comes to hydrophobic, fat-soluble substances. This characteristic could be valuable from a medical point of view but may add to the potential for bioaccumulation.

1.1.2 Ways that pharmaceuticals enter the environment

Most commonly, APIs enter the environment through (see Figure 1):

- Release from production facilities
- Excretion from humans or animals using medicines
- Inappropriate disposal of medicines waste (including unused medicines).

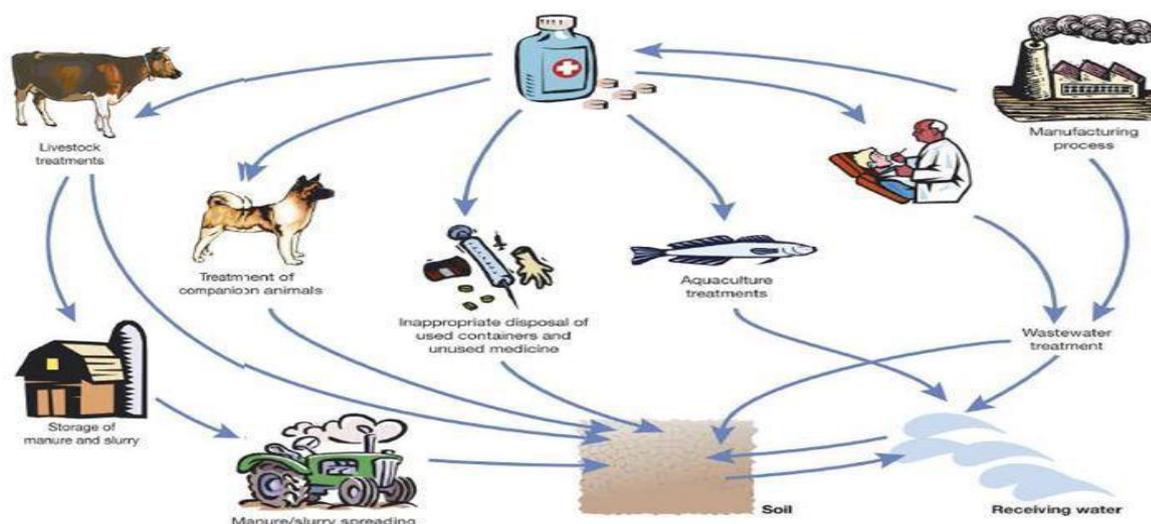


Figure 1: APIs' different ways into the environment.⁵

1.2 Negative environmental effects of pharmaceuticals

Residual APIs may have an effect on many living organisms. Research from both laboratory and field studies have confirmed that APIs might cause negative effects in exposed organisms at concentrations currently observed in some aquatic environments. APIs such as hormones or those affecting the nervous system have been observed to cause adverse effects in fish and tadpoles,⁶ and to result in the expression of candidate genes influencing behaviour in fish.⁷ The most serious effect of exposure to hormones in the environment is the disturbance of reproduction, and this could even lead to a population collapse.⁸

Problems related to hormone action can be described as follows:

- 1) Some APIs have hormonal activity and may potentiate the action of hormones.
- 2) Some APIs may antagonise the action of hormones.
- 3) Hormones and APIs with hormonal activity may act at relatively low concentrations.
- 4) Hormones naturally derived from humans and animals also flow into the environment.
- 5) APIs might act synergistically. (APIs that express effects through the same receptor show a similar interaction. In order to understand the threshold leading to the onset of action, further research is needed on appropriate evaluation methods and the criteria for the combined action.)

Some psychotropic medicines act on receptors that hormones also act on, so they may also have negative environmental impacts. For instance, a study⁹ on the effects of atenolol, a β -adrenergic receptor antagonist, showed low toxicity with embryo-larval development (early life stage) in fish, considering the real environmental concentration was low.⁹ The study⁹ shows that on the basis of the actual environmental concentrations, chronic toxicity may be of little account. Although this is an important finding, effects due to exposure to low concentrations in the long term are not yet clear because these conclusions were derived from results of exposure of a relatively short time. More research is required.⁹

The effects observed after exposure to psychotropic medicines resulted in behavioural changes that, in the long term, may lead to negative effects on fish populations.¹⁰

A striking example of a negative environmental effect of a medicine is the population collapse of vultures that fed on the corpses of diclofenac-treated animals in the Indian subcontinent.¹¹

A growing concern is that the release of residual antibiotics into the environment may contribute to antibacterial resistance.¹² Since the purpose of antibiotics is to destroy or control microorganism populations, the risk of disturbing the balance of microorganisms in the ecosystem is large. Algae, as a producer in ecosystem, are especially shown to be highly sensitive to antibiotics.¹³ After medicines are administered non-metabolites and metabolites are excreted, and those compounds end up in sewage treatment plants. There, the compounds may have a negative effect on the bacterial flora of activated sludge, leading to a reduction in their decomposition by microorganisms and their eventual release into public water systems.¹³

Some medicines, such as carbamazepine, have been detected in relatively high concentrations in effluent from sewage treatment plants. It is difficult to reduce these medicines not only in sewage treatment plants but also in the ecosystem. A concern over ingestion through drinking water that is purified from raw water containing APIs has been identified.

Current scientific understanding of the environmental risk of pharmaceutical residuals is incomplete and our ability to measure low concentrations of APIs can still be improved. Nevertheless, based on the concepts of the *precautionary principle*^{14,15} which encourages anticipatory action in public health and environmental decision-making, even in the absence of scientific certainty: “When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically.” Efforts need to be made to reduce the unintentional release of APIs into the environment.

1.2.1 Risk assessment data gaps and opportunities

Historically, environmental contamination risk-assessment methodologies have been developed from needs assessments and were used to manage risks posed by pesticides, heavy metals and persistent organic pollutants. They have also been used to assess environmental risks from industrial chemicals, and similar methodologies are applied to pharmaceuticals.

However, pharmaceuticals differ from many of the historical contaminants for which environmental toxicology tools were developed.

Since the majority of pharmaceuticals possess relatively low acute-toxicity profiles, particularly within the concentration levels (ng/L to µg/L) typically observed in surface waters, employing tools used to assess the acute toxicity of non-pharmaceutical contaminants has been questioned.

1.2.2 Environmental classification of APIs and finished pharmaceutical products

Two examples of initiatives by the Research-based Pharmaceutical Industry in Sweden (LIF) show how to analyse and provide information on the environmental properties of APIs and finished pharmaceutical products to prescribers, pharmacists, users, purchasers and others. There are two environmental classification schemes:

- An environmental classification of APIs (implemented in 2005)
- An environmental assessment of pharmaceutical products (under development)

Environmental classification of active pharmaceutical ingredients

In 2004, LIF began an initiative to develop an environmental classification scheme for APIs.¹⁶ The environmental information draws on data from pharmaceutical companies, often generated in the preparation phase of environmental risk assessments. An independent organisation, the Swedish Environmental Research Institute (IVL) reviews all data, assessments and classifications. The environmental information and classifications of different APIs can be found in the Swedish prescribing guide Fass.¹⁷

The inherent environmental hazard of an API lies in its toxicity, its biodegradability and its potential to bioaccumulate. An API that is considered highly potent and toxic may not necessarily pose the greatest environmental risk. Less potent and less toxic substances used in greater quantities may result in higher environmental risks. That is why it is important to distinguish between environmental risk and environmental hazard:

$$\text{Risk} = (\text{Hazard}) \times (\text{Exposure})$$

To assess whether an API poses an environmental risk or not, the highest concentration of that API that is expected not to cause negative effects in animals and plants (the so-called predicted no-effect concentration [PNEC]) should be investigated first. The PNEC is compared with the predicted environmental concentration (PEC). The PEC/PNEC ratio gives a number between zero and infinity. As long as the PEC/PNEC-ratio is below 1, the risk is regarded as insignificant or low and to be under control.

In addition to the risk (based on the PEC/PNEC-ratio), the Swedish API environmental classification scheme also reports on biodegradability and the potential for bioaccumulation.

Environmental assessment of pharmaceutical products

The classification scheme presented above does not allow for differentiation among different products containing the same API.

LIF has been commissioned by the Swedish government within its National Pharmaceutical Strategy to develop an environmental assessment model for pharmaceutical products. The model should enable differentiation between products with the same API, and include environmental aspects from the life cycle of the product, e.g. from manufacturing operations.

Two areas of environmental concern are included in the model proposal: “effective management of API residue from the manufacturing process” and “materiality analysis, carbon footprint and other environmental resource measures”.

Physicochemical and biological properties and the regulatory assessment toolbox

Unlike non-ionisable persistent organic pollutants, most pharmaceuticals are either weak acids or weak bases and thus may be ionised across the pH ranges found in surface water. Variations within this pH range can, therefore, influence the bioavailability and toxicology of pharmaceuticals within ecosystems. This area represents an active field of study, particularly since urbanisation and climate change can modify the pH of surface waters and thus influence site-specific environmental risks of pharmaceuticals.

In addition, physicochemical properties of pharmaceuticals can have a strong influence on their partitioning within various environmental compartments (e.g. water, sediment, soil, biological tissues) and thus affect exposure and risk estimates for non-target organisms.

Comparative pharmacology/toxicology

Developing appropriate tools to assess sub-lethal effects of pharmaceuticals in the environment represents a pressing research need. Sub-lethal effects in aquatic organisms have received extensive study in recent years.

Fortunately, pharmaceutical safety data, particularly for new entities or generic medicines, are much more extensively available than for other industrial chemicals. Such mammalian pharmacology and toxicology information may be used to identify organisms in the environment potentially at highest risks of various pharmaceutical mechanisms of action. Regulatory agencies have started to adopt additional testing requirements based on this information.

Lessons learnt from the study of pharmaceuticals in the environment ensure advancing environmental risk-assessment approaches for other industrial chemicals. For example, a relatively limited number of adverse outcome pathways associated with non-pharmaceutical contaminants have been extensively studied. The development of an advanced understanding of adverse outcome pathways in the environment associated with pharmaceutical mechanisms of action would significantly advance the science of mechanistic and predictive ecotoxicology for other contaminants. The application of such information to identify chemicals with elevated hazard profiles, and thus requiring environmental management, appears promising.

Tox21 approach to elucidate targets, resulting in adverse outcome pathways

Comprehensive programmes, such as the US EPA’s Tox21^a programme,¹⁸ are collecting extensive toxicology data for industrial chemicals, including some pharmaceuticals. This information is being actively used to develop computation toxicology tools to aid in identifying structural attributes of chemicals, including pharmaceuticals, with potential adverse outcome pathways in the environment. Lessons learnt from pharmacological safety assessments are being applied to support regulatory initiatives.

1.3 Current impact and future trends

1.3.1 Changes in population lifespan, demographics and distribution

Landscapes are changing as demographic transitions, population growth and urbanisation occur on a global scale. Human interactions with water resources, energy production and food supplies form a complex web that

^a The Tox 21 programme is pooling federal resources to use robotics technology to screen thousands of chemicals for potential toxicity, using screening data to predict the potential toxicity of chemicals and developing a cost-effective approach for prioritising the thousands of chemicals that need toxicity testing.

requires careful management to achieve sustainability. Developing sustainable practices for natural resource management during economic development while balancing health care demands will inherently influence the fates of human societies.

Lifespans are increasing in many parts of the world as a result of more effective delivery of public health services. From life-saving medicines to maintenance therapies that improve quality of life, pharmaceuticals reduce mortality and increase life expectancy, particularly in patients over 60 years old.¹⁹ Between 2010 and 2050, the World Health Organization is predicting 188% and 351% increases in the world's population exceeding 65 and 85 years of age, respectively.²⁰ In developed countries, people aged 85 years or more often represent the fastest growing proportion of the population.²⁰ With an aging population comes an increased use of medicines. For example, a hospital in Ontario, Canada, shows an average of 15 medicines taken daily by each patient (51 individuals; mean age 81 years).²¹

More people now live in cities than ever before. The United Nations projects that, by 2050, the world population will reach 9.6 billion²² and 70% will live in urban areas.²³ Such a concentration of the population presents a number of emerging challenges to sustainable protection of public health and the environment. In the USA, diversion and abuse of unused medicines is considered to be at epidemic levels by the Centres for Disease Control and Prevention.²⁴ Given the levels of non-adherence, and that medicines are not always managed as effectively as they could be, there is a high level of waste, evidenced by the fact that around 11% of UK households have one or more medicines that are leftover.²⁵ To solve the problem of leftover medicines in households and diminish the risks they pose, unused medicine take-back or collection programmes have been developed by some countries. The pharmacist practitioner has the opportunity to influence more rational prescribing that would reduce the amount of leftover medicines. This would decrease potential risks to the environment as well.

1.3.2 Growing demands on environment and water supplies

When consumed and unused medicines are disposed of through wastewater treatment systems, residues of pharmaceuticals may be introduced into the environment. The magnitude of pharmaceutical contamination of surface waters depends on the quality of treatment technologies available, which varies widely among both developed and developing nations. Water supplies are of particular relevance to urbanising regions, where elevated population densities depend on sufficient quantity and quality of water to sustain agricultural, industrial, ecological and potable needs. The need for new water supplies in urbanising watersheds, and associated water and wastewater treatment infrastructures, results in river flows influenced by or even dependent on discharges of reclaimed wastewater.²⁶ When these sources for water become arteries for beneficial reuse, an urban water cycle is observed.²⁷ Water reuse (i.e. the recycling of treated wastewater) is increasing in many regions experiencing rapid population growth,²⁸ something that is particularly relevant for regions susceptible to short- and longer-term extremes of climate.

Furthermore, a combination of demographic transitions, economic development, population growth, and urbanisation signals the continued rise in pharmaceuticals usage, which will become more concentrated, particularly in megacities. Developing intervention programmes to manage the environmental footprints of pharmaceuticals presents an important opportunity for achieving sustainable environmental quality goals.

2 Solutions

2.1 Eco-adapted approach for pharmaceuticals

In the face of increasing evidence that pharmaceuticals, from research and production to disposal or metabolism, are posing a threat to the environment that is bigger than previously thought there is clearly a need for action. Societies' current responses to the environmental burden caused by the health sector is low and pharmacists are well positioned to change the way citizens look at their own medicines use.

The implementation of effective eco-adapted approaches for pharmaceuticals and health care waste management programmes requires multi-sectorial cooperation and interaction at all levels. Policies should be generated and coordinated globally, with management practices implemented locally. Establishment of a national policy and a legal framework, training of personnel, and raising of public awareness are essential elements for success.

Improved public awareness of the problem is vital in encouraging community participation in generating and implementing policies and programmes to reduce the environmental impact of medicines.

Diminishing the negative impact of pharmaceuticals in the environment and environmentally adapted management of health care waste should thus be put into a systematic, multifaceted framework, and should become an integral feature of health care services.

2.2 Sustainable policies/framework

United Nations joint programme on Green Procurement in the Health Sector

With the overall objective of reducing the environmental burden caused by the health sector, six United Nations agencies (United Nations Development Programme [UNDP], United Nations Environment Programme [UNEP], United Nations Population Fund [UNFPA], United Nations International Children's Emergency Fund [UNICEF], United Nations Office for Project Services [UNOPS] and World Health Organization [WHO]) have started a joint programme on green procurement in the health sector that began in 2013 and will run to 2017.²⁹

This will serve as a strategic tool to influence UN agency procurement, practitioners, suppliers and funding entities to adopt and apply less environmentally harmful procurement practices, manufacturing processes and products. The approach to achieving this UN objective is to take stock of current initiatives and coordinate new activities in a streamlined manner, aiming at more sustainable procurement practices of the UN agencies' own operations. The UN has a critical mass of procurement in some segments of the market that could help orient the market towards more sustainable directions.³⁰

WHO and UNEP Health and Environment Linkages Initiative

The environment is a major determinant of health. Environmental hazards are responsible for an estimated 25% of the total burden of disease worldwide, and nearly 35% in regions such as sub-Saharan Africa,^{31,32} and for almost 20% of all deaths in the WHO European Region. The WHO works together with UNEP to support action by developing country policymakers on environmental threats to health in a global effort called the Health and Environment Linkages Initiative (HELI).³³ HELI encourages countries to address health and environment linkages as integral to economic development, and supports valuation of ecosystem services to human health and well-being — services ranging from climate regulation to provision/replenishment of air, water, food and energy sources, and healthy living and working environments in general. HELI activities include country-level pilot projects and refinement of assessment tools to support decision-making.

Regional policies

In 1989, concerned about the growing evidence of the impact of hazardous environments on human health, WHO/Europe initiated the first-ever environment and health process that would work towards a broad primary prevention public health approach and facilitate inter-sectorial policymaking.

The WHO-AFRO Environmental Health Policy (EHP) programme aims to assist countries in the AFRO region in their endeavour to achieve sustainable development by creating an environment conducive to health through the establishment of the Environmental Health Policy and strengthening/developing their capacities to render sound Environmental Health Services.³⁴

The European Parliament and the Council of the European Union approved in November 2013 the “Union Environmental Action Programme to 2020”. The EU has agreed to step up its efforts to protect our natural capital, stimulate resource-efficient, low-carbon growth and innovation, and safeguard people’s health and well-being — while respecting the Earth’s natural limits. It is a common strategy that guides future action by EU institutions and member states that share responsibility for its implementation and the achievement of its priority objectives. The programme lists nine priority objectives and what the EU needs to do to achieve them by 2020. They are to:

1. Protect, conserve and enhance the EU’s natural capital;
2. Turn the EU into a resource-efficient, green and competitive low-carbon economy;
3. Safeguard EU citizens from environment-related pressures and risks to health and wellbeing;
4. Maximise the benefits of EU environmental legislation by improving implementation
5. Increase knowledge about the environment and widen the evidence base for policy;
6. Secure investment for environmental and climate policy and account for the environmental costs of any societal activities;
7. Better integrate environmental concerns into other policy areas and ensure coherence when creating new policy;
8. Make EU cities more sustainable;
9. Help the EU address international environmental and climate challenges more effectively.

The Environment Action Programme also sets out a long-term vision of a non-toxic environment and proposes to address risks associated with the use of chemicals in products and chemical mixtures, especially those that interfere with the endocrine system. In parallel, a more predictable framework combined with more investment in knowledge is intended to encourage innovation and the development of more sustainable solutions.^{35,36}

Environment requirements in the public procurement of medicines have existed for more than 10 years in Sweden and have been supplemented with social sustainability requirements during recent years. The procurement of medicines is made via tender processes by Sweden’s 21 county councils. The county councils have jointly agreed to base their sustainability criteria on a numbers of requirements developed by the Swedish Environmental Management Council (SEMCo)³⁷ in collaboration with relevant stakeholders.

National policies

Several national policies on managing pharmaceutical waste have been introduced. For example, the Resource Conservation and Recovery Act (RCRA) in the USA, enacted in 1976, is the principal federal law governing the disposal of solid waste and hazardous waste.^b The USA also developed a federal list of “hazardous drug exposures in health care” that focuses on employee safety.³⁸ Standards for “hazardous drugs — handling in health care settings” are currently being written.³⁹

FIP/WHO Joint Guidelines on Good Pharmacy Practice — Standards for Quality Services

Pharmacists are increasingly responsible for the medicines use process, and it must be recognised that waste management is a part of that process. As highlighted in the FIP/WHO Joint Guidelines on Good Pharmacy Practice — Standards for Quality Services,⁴⁰ a pharmacist’s role is to prepare, obtain, store, secure, distribute, administer, dispense and, importantly for the purpose of this document, dispose of medicinal products.

This role is described as:

“Dispose of medicine preparations and medical products

Minimum national standards should be established for these activities.

- *Pharmacists should ensure that regular monitoring of the medicines inventory is conducted and should always include medicines samples in the process of periodic inspection for expiration dates and removal of outdated stock.*

^b Resource Conservation and Recovery Act, P.L. 94-580, 90 Stat. 2795, 42 U.S.C. § 6901 et seq., October 21, 1976

- *Pharmacists should ensure that recalled medical products, including medicines samples, are immediately stored separately for subsequent disposal and prevented from being available for further dispensing or distribution.*
- *Pharmacists should establish a safe way of medicines waste disposal at the hospital or community pharmacy so that patients and the public are encouraged to return their expired or unwanted medicines and medical devices. Alternatively, pharmacists should provide appropriate information to patients on how to safely dispose of expired or unwanted medicines.*

This guidance is recommended as a set of professional goals to be met in the interest of the patients and other key stakeholders in the pharmaceutical sector. Responsibility for moving the project forward will rest with each national pharmacy professional association. Achieving specific standards of GPP for each nation within these recommendations may require considerable time and effort. As health professionals, pharmacists have a duty to begin the process without delay.”

Green pharmacy practice concept

Daughton⁴¹ proposed the need for “green pharmacy”, where the life cycle of pharmaceuticals — from “cradle to grave”, including synthesis from raw materials, production of products, transportation, storage, deliveries, usage, and disposal — is appropriately assessed, anticipated and managed. Clearly, pharmacists and pharmaceutical scientists must contribute to achieving a greener pharmacy.

2.3 Pharmacists’ role in different practice settings

Pharmacists are experts in the proper use of medicines. Therefore, it is important that they accept responsibility for the entire medicines-use process — from prescription and selection to disposal and waste.

The recognition of pharmacists’ responsibility for optimal medication use has continued to spread throughout the global pharmacist community since its first enunciation in 1990. Historically, the pharmacist has always accepted responsibility for the correct and safe distribution of medicines in the dispensing process. The growing involvement in the clinical management of medication use — variously called pharmaceutical care or medication management — is driven by societal need and facilitated by the pharmacists’ clinical education.

There is a great opportunity for the profession and the pharmacist practitioner to provide substantial leadership in the resolution of the environmental issues that surround medicines use. This leadership begins with a universal professional acceptance of the pharmacist’s responsibility for the management of the medication, which includes minimising the environmental impact that medicines can have by proper disposal of unused products.

As custodians of medicines, pharmacists are part of the problem. But they can also be part of the solution by discussing environmental issues with prescribers and consumers. Pharmacists in many jurisdictions have the opportunity to work with other providers to prescribe medicines that balance effectiveness and minimise environmental risk. In institutions, hospitals, or any clinical practice, pharmacists can provide environmental-risk assessment advice to other practitioners and staff. This function can overreach patient-care areas and also include selection, purchasing and procurement of medicines.

Also, pharmacists who work in the management of health-maintenance organisations, insurance programmes and governmental health-benefit programmes have the opportunity to take the environmental risks of medicines into consideration when designing formularies or approved medicines lists.

There is an increasing move towards schools and colleges of pharmacy developing curricula to inform potential pharmacists of their environmental responsibilities while encouraging relevant behaviours for them to exhibit when at practice sites.

Pharmacists’ positive environmental impact will vary depending on the setting in which they practise:

- Green hospital and institutional practice
- Green community and ambulatory practice
- Consumers of medication
- Green pharmaceutical industry
- Green distribution, warehouses and offices.

The following chapters will provide a detailed look at each of these practice settings.

2.3.1 Green hospital and institutional practice

In hospitals and institutions, pharmaceutical waste is generated most commonly from partially used vials (from sterile compounding), partially used and unused intravenous solutions, partially used ointments, inhalers or other multi-use items, including insulin vials, and expired medicines.

These items can become waste within the (hospital) pharmacy or in any treatment location within the institution. It is, therefore, important for pharmacists to develop programmes that reach beyond their pharmacy/department in the institution. Managing pharmaceutical waste in patient-care units is the most difficult challenge because of the greater number of staff and wider variety of situations that can occur.

There are several steps that can be taken to minimise the environmental impact of pharmaceuticals in hospitals and institutions.

Familiarity with laws and governmental rules or regulations

It is important to be aware of any current governmental rules or regulations that apply to waste pharmaceuticals. These are sometimes embedded in more general regulations for chemical wastes. Pharmaceuticals may have already been addressed at the regulatory level and clear guidelines may already be available. Some examples have been provided in the survey results that were obtained as part of this research. [Appendix 1](#) of this document shows example environmental policies and practices in the pharmacy at Helsinki University Central Hospital.

Complying with regulations

After becoming familiar with the regulations, it will be necessary to determine how to contain waste pharmaceuticals in a manner that complies with them.

Pharmaceutical waste containers should be spill-proof, leak-proof and meet any government collection and transportation standards. There are a number of vendors that specialise in containing chemical wastes and some that provide specific pharmaceutical waste containers. The next step is to determine the options for treatment and disposal.

High-temperature incinerators are considered optimal to ensure destruction of all pharmaceuticals prior to emission into the atmosphere. This option depends on the air emission regulations. Medicines containing mercury or halogens are sometimes treated using different processes and may need to be segregated. Waste-to-energy incinerators may be available. These burn municipal garbage and generate energy back to the community. They are considered a “green technology” and can usually accept most pharmaceutical waste, although chemotherapy may be prohibited due to the “open pit” feeding system used. Some countries also have regulated medical waste incinerators that are used for some or all potentially infectious waste, usually referred to as “biohazardous”, “potentially infectious” or “red bag” waste. These can often accept most pharmaceuticals also.

Many of the sharps containers in which needles are now discarded are autoclaved. This is not a particularly good solution for medicine waste, since the process often releases the medicines into the sewer system. Disposal in the sewer by the hospital would accomplish the same end but is not an optimal solution since one of the goals of a pharmaceutical waste management programme is to keep medicines out of the water system.

Disposal in a properly managed landfill is probably the next best option if no incineration facilities are available. These must be lined and well managed, however, to ensure both security of the medicines from diversion and leakage into the surrounding ground water. Some countries have employed open burning, which makes the medicines unrecoverable but causes air pollution, or treatment with bleach, which often destroys the APIs but then must be managed carefully to avoid additional pollution.

Segregation of waste

Based on both the country’s regulations and the waste-disposal technologies that are available, waste pharmaceuticals may or may not need to be segregated into multiple categories. For example, due to the hazardous nature of chemotherapy medicines, these often need special handling and treatment from other less toxic pharmaceuticals. This evaluation should include input from experts in the waste management field. Ideally, the national or regional pharmaceutical association could work with content experts to develop guidance, if it does not exist already.

Provision of guidance information

Setting up a pharmaceutical waste management programme in the pharmacy department is only the first step. Since most pharmaceutical waste is generated in the patient care areas, the real challenge is to develop a programme that nursing staff and others who handle medicines can easily understand and follow. Not only can these be intense and high stress areas for staff, but also many different types of pharmaceutical waste are generated. If nursing staff needs to segregate medicines into more than one container, pharmacy will need to take the lead in providing guidance for the proper disposal for each medicine. Ideally, if there are electronic systems in place for order entry, a message can be placed into the nursing charts indicating which medicines require special handling.

To successfully implement a sustainable, compliant pharmaceutical waste management programme in a hospital, it will be necessary to develop a multidisciplinary team that can understand and develop the process from start to finish. The final plan will vary depending on the jurisdiction and the facility, but the goal should be cost-effective practices that result in fewer medicines in the water supply and less air pollution.

Prevention of further contamination

Items such as personal protective equipment that is worn or used in the preparation of chemotherapy should also be managed by incineration whenever possible, to prevent contamination in the immediate patient-care area. These can be sent to a regulated medical waste incinerator, which is sufficient to destroy any residual molecules of chemotherapy.

Prevention and waste minimisation

Waste minimisation is always the best practice, from both an environmental and economic perspective. One of the best ways to ensure medicines do not become waste is to develop efficient stocking and ordering methods that reduce the number of medicines that become outdated or unused. If a facility is in a position to receive donated medicines it is worthwhile to accept only medicines that are needed and have sufficient use time remaining.

While working with a hospital or other institution, all the metabolites that patients, staff and other members of the community are excreting into the wastewater system should be taken into consideration. It is likely the local wastewater treatment plant was designed to remove sediments and pathogens, but not necessarily medicines and their metabolites. One way to address these issues is to work towards life style changes, such as weight loss and exercise, which may reduce the number of drugs needed by individuals. Another is to encourage patients and providers to be aware of relative hazards of prescription options — and to choose the least hazardous and most effective medicine.

2.3.2 Green community and ambulatory practice

Community pharmacies are the main health care facilities used by the public to access medicines. Community pharmacies are also the most visited points of primary health care. Pharmacists' education allows them to understand the effects that medicines and their metabolites might have in the environment. This gives the pharmacist important opportunities to inform consumers about the environmental impact of medicines and the importance of correct use and disposal of waste.

To prevent unused medicines from accumulating in homes, rational prescribing and dispensing in appropriate quantities are important, especially when a new medicine is started. With effective stock management, it is possible to minimise the amount of expired medicines in the pharmacy. The premises and processes in the pharmacy should be organised so that environmental aspects are taken into consideration. Community pharmacists can also play an important role in informing prescribers about the environmental classification of medicines so that they can consider the relative impact when prescribing.

Information to consumers

Consumers should be informed about the hazardous nature of pharmaceutical waste and the need for proper disposal. Information regarding the right way to dispose of pharmaceutical waste and about available collection programmes by the pharmacy should be provided to consumers. Specific information about pharmaceutical patches (as they are not empty at the time of disposal) and the ways that medicines should be packed for the collection programme also needs to be given.

In those countries that have environmental classifications of prescription medication, the pharmacist should incorporate a discussion of the programme and its importance in reducing pollution into pharmaceutical care

visits. Pharmacists should work with prescribers to choose the appropriate medicines that minimise potential environmental risks without jeopardising patients' needs and patient safety.

The instructions and legislation regarding how medicines are classified as waste, how households are instructed to dispose of pharmaceutical waste and pharmacies' role in the collection programmes vary from country to country. [Appendix 2](#) of this document shows an example of pharmaceutical waste management in the USA.

Accreditation in environmental management

If a pharmacy wants to reach an accredited status with its environmental management system, there are several accreditation possibilities in place. The ISO 14001 series from year 2004 is the internationally recognised standard concerning environmental issues. There are also regional standards such as the EU model EMAS,⁴² which a company can use to determine its environmental responsibilities. Accreditation is an expensive process and may be realistic for big companies only. However, the information in these standards can be used without official accreditation: they provide a systematic approach to look at the environmental issues.

The process starts with analysing pharmacy procedures and looking at the different kinds of potential environmental problems these procedures may cause. The pharmacy should consider how significant these problem areas are and determine what it can do to minimise the risk. In hospital practice, the entire facility must participate in the process.

This process can be done in every pharmacy. *Table 1* gives an example of environmental risks in a community pharmacy in Finland.

Table 1: Example of a risk analysis in a community pharmacy

RISK ANALYSIS IN A COMMUNITY PHARMACY					
ACTIVITY	ISSUE	EFFECT ON ENVIRONMENT	IMPORTANCE OF RISK	WHAT WE CAN DO	INDICATORS
Paper usage	Garbage: paper and cardboard, confidential material	Adds to unnecessary landfill	++	Collection of waste, recycling	Monitor paper usage, follow up of the amount of confidential material
Premises	Electricity, water, heating	Effect on waste water and climate	+	Modern technology (less consumption of energy), closing all machines for night, effective cleaning, central heating and cooling with optimal temperatures	Monitor electricity bills, change of equipment
Storage	Optimisation of storage	Unused medicines are a cost for disposal processes	+	Effective storage management	Amount and value of expired products
Equipment	Batteries and fluorescent lights	Used batteries and fluorescent lights are a cost for disposal processes	+	Collect and take to proper discharge place	Exchange intervals of fluorescent lights
Cleaning	Towels for single use	Unnecessary landfill	+	If possible, usage of multi-use towels	Follow-up of towel usage
Eating	Packaging materials, biowaste	Unnecessary landfill and impact to atmosphere	++	Sorting and recycling	
Logistics	Logistical problems	Traffic emissions	+	Suppliers use same transport system	
Customers	Packaging materials	Unnecessary landfill	+	Customer information, ask if plastic pack is needed, we do have linen bags	Frequency of plastic bag orders
Customers, return of unused and expired medicines	Medical waste	Environmental problems if not discharged properly	+++	Support of adherence, rational use of small packages, information to customers, recycling information	The amount of returned medicines per year
Physicians, prescribing habits	Environmental risks	Toxic effects on the environment	+	Information to other health care providers. National guidelines on prescription	Actions taken

Table 1 shows that the most important issues for the pharmacy are to improve medication compliance so that all medicines dispensed are actually used by the consumer, as well as participating in collection programmes. There should be a procedure for managing each issue, as highlighted in the Table.

It is also important to be able to measure the success of the different actions taken. One can measure the amount of waste collected, the amount of electricity used, the consumption of paper, etc.

The risk analyses are made at two- or three-year intervals to follow the development of the programmes. It is also possible to publish an environmental report based on the pharmacy's activities and use it to further raise general awareness of environmental issues in the public the pharmacy serves.

Prevention of excessive consumption

Inappropriate and excessive consumption of pharmaceuticals is one of the causes of unnecessary emissions. Overconsumption of medicinal products can start at the time of purchase or prescribing and continue during administration. Through consultations and appropriate prescriptions, prescribers are responsible for assessing the actual needs of each patient.³

Studies related to the treatment of infections show that patient satisfaction in primary care settings depends more on effective communication than on receiving a prescription for antibiotics.^{43, 44, 45} Rutten *et al.*⁴⁶ observe: "Professional medical advice impacts [on] patients' perceptions and attitude towards their illness and perceived need for antibiotics, in particular when they are advised on what to expect in the course of the illness, including the realistic recovery time and self-management strategies." The aim is that patients use medicines only when necessary and adhere to their treatment. Pharmacists, owing to their privileged relationship with patients,³ are well positioned to provide such effective communication and increase adherence.

However, in some countries, some medicinal products can be sold without professional advice or supervision. It is common for people to self-medicate when having mild pain and headaches, colds and allergy symptoms, and gastro-intestinal upset or discomfort, although these practices vary from one country to another. Some medicinal products can be sold over the counter in some countries with or without the supervision of a pharmacist³ (or in petrol stations, super markets, etc.), whereas a prescription would be needed elsewhere.^{47, 48, 49}

Beyond the actual need for medication, consumers are in some countries confronted every day by advertisements for medicinal products, tailored to sub-populations, seasonal diseases and discomfort. Demand for medicinal products and their (over)consumption may therefore be stimulated through marketing strategies, especially if access to those products is not supported by access to the medicines expertise that pharmacists are well positioned to provide.⁵⁰

Ensuring the combination of access to self-medication and OTC products with access to pharmaceutical expertise is, therefore, one way of preventing excessive and inappropriate consumption of medicines and decreasing unnecessary emissions.

Implementation of collection schemes for unused medicines

To prevent the accumulation of unused or partially used medicines in households, medicines, especially newly prescribed medicines, should be dispensed in small (starter) packages and unit-of-use dispensing should be encouraged. The amount of unused medicines that becomes waste should be minimised and pharmacists should support adherence and rational use of medicines not only for patient benefit but also because of environmental concerns.

Collection schemes for unused medicinal products represent one of the simplest ways, with great potential, to reduce inputs of pharmaceutical products into the environment.³

Regulations on unused medicines exist within several markets around the world. For instance, under Article 127b of EU Directive 2001/83/⁵¹ all EU Member States "shall ensure that appropriate collection systems are in place for medicinal products that are unused or have expired", however, there is no harmonised take back system imposed at the EU level. As a result, collection schemes are inconsistent from one EU Member State to another. Collection schemes had been established in 20 European countries by 2009.⁵²

According to the European Environmental Agency⁵³ the best way to organise a collection programme for pharmaceutical waste is through pharmacies. All pharmaceuticals dispensed by a pharmacy should be labelled with "Return unused medicines to a pharmacy" provided that pharmacies in the country offer such a service.

If the pharmacy is running a collection programme, it will need an agreement with a company (e.g. a wholesaler) that collects and disposes of the pharmaceutical waste. The agreement should specify:

- How the waste will be packed by the pharmacy;
- Who will check that the repacking is correct;

- Who will inform customers about the collection programme;
- Who will prepare transport documents and documentation of transport;
- What type of collection containers, their size and models, will be used;
- How often the containers will be emptied;
- What are the responsibilities of the different actors;
- Who is responsible for the costs of the service.

The conditions vary depending on national waste management legislation. In [Appendix 3](#) there are model agreements, model transport documents and model patient information leaflets.

Customers have to follow the instructions given by the pharmacy about repackaging the pharmaceutical waste. The pharmacy must retain a right to refuse medicines offered for return, in case the customer cannot identify them. [Appendix 3](#) shows an example of information for customers about a collection programme.

With human medicines, whatever the type of organisation in charge of collection schemes (e.g. government-owned companies, environmental non-profit organisations, pharmaceutical federations, etc.), pharmacists are the key players in the collection of unused medicines because of their privileged relationships with patients.⁵⁴ ^{55, 56} Their systematic involvement would benefit the collection of unused medicines.⁵⁴ Yet, the collection of unused medicines may just represent a supplementary constraint for them so far.⁵⁴ In order to increase the implementation and efficiency of collection schemes for human medicinal products, pharmacists' responsibilities could be clarified and better used within collection initiatives. Some countries, like France and Norway, have even made their participation mandatory.³

Furthermore, better communication, within pharmacies and retailing points, could further help increase awareness of such schemes. Providing streamlined information to patients regarding the importance and current efficiency of the collection of unused medicines could increase awareness and modify practices accordingly.³

There are positive examples of pharmacists having an active role in the collection of unused medicines. In Australia there is a government-supported initiative called Return of Unwanted Medicines (RUM)⁵⁷ which ensures unused medicines collected from community pharmacies are safely disposed of. Pharmacists in France, Slovenia and South Africa have established unused medicine disposal programmes. Education campaigns have been organised in some countries regarding the proper disposal of leftover medicines. Pharmacists organised collections of expired and unused medicines, for instance, by appointment with pharmacists in Malaysia or by bringing the medicines to the pharmacy directly (e.g. France, Portugal, Spain, Slovakia).^c In the United States, new Drug Enforcement Administration regulations^c enable all unwanted medicines to be collected through pharmacy kiosks, law enforcement offices or highly controlled mail-back programmes.⁵⁸

2.3.3 Interprofessional collaboration

Information to other health care providers

The environmental effects of pharmaceuticals are not well known among health care providers, including pharmacists. Experience demonstrates that informing physicians and other prescribers will contribute to modification of practices affecting the emission of APIs into the environment. Pharmacists are well positioned to increase awareness of these environmental issues by informing local physicians, nurses and home health care providers. Besides the therapeutic effects, pharmacists are also in a good position to discuss environmentally adapted choices with prescribers and patients and to inform them about the impact of prescribing small quantities (starter packages) when starting a medicine, and the benefits of unit-dose or unit-of-use dispensing. There are many possibilities for collaboration among health care providers. Even though the issues surrounding the release of pharmaceuticals and their metabolites into the environment is relatively unknown by the various providers, they generally take an interest when the issues are presented to them. National pharmaceutical associations are in a good position to take the lead on these issues by informing other organisations and producing material for articles and local presentations for use by their members.

^c According to national regulations, e.g. in USA it is Drug Enforcement Administration regulations, available here: http://www.deadiversion.usdoj.gov/drug_disposal/

Sustainable prescribing

A study⁵⁹ has revealed that many medicines could be prescribed at lower doses than indicated on the label and still achieve therapeutic endpoints. Lower-dose prescribing is a viable means of reducing the ultimate excretion of APIs into sewage as well as reducing the incidence of leftover medicines that might be disposed of via sewers (partly as a result of lowering the occurrence of dose-related adverse events in patients).⁵⁹

“Eco-Directed Sustainable Prescribing” is an approach to pollution prevention that could also result in substantial collateral benefits for health care. These potential collateral benefits include: improving therapeutic outcomes, reducing patient expense, minimising medicines wastage (and thereby the subsequent need for disposal), and reducing morbidity and mortality from accidental poisonings caused by improperly stored or disposed of medicines. Imprudent drug use (inappropriate, non-optimal selection of a specific medication and the use of unnecessarily excessive doses) is a major aspect of escalating national health care costs — which, overall, consumes an unsustainable 17% of gross domestic product on global average. Eco-Directed Sustainable Prescribing could play a role in reducing a portion of this drain on the economy and at the same time protect the environment, improve healthcare and prevent avoidable human poisonings.^d

2.3.4 Pharmaceutical industry

Obligation of the industry

The pharmaceutical industry has, like all other players active in society, an ethical, and to a certain extent, a legal obligation to ensure that its operations are sustainable in an environmental context. All activities should be performed with lowest possible environmental impact. In other words, the pharmaceutical industry should do its part when it comes to realising the concept of green pharmacy.

It is probably clear to everyone that pharmaceutical products have improved the quality of life for billions of people around the globe. The health benefits to society, individual patients and other consumers are evident. Properties, characteristics and effects of the active substances as well as of the final products are well documented throughout preclinical and clinical research and development processes. The positive effects on health, as well as potential adverse effects from treatment, are also monitored post-authorisation.

Research and development, manufacturing, marketing, and sales are all examples of industry operations where environmental perspectives are relevant. Also patent and pricing policies have environmental dimensions. Green economic incentives in pricing and reimbursement systems and green procurement without jeopardising patient needs and patient safety, are examples of initiatives that support industry’s green journey.

Society can support the industry’s green journey through two initiatives:

- Legal requirements that establish a level playing field for all competitors — globally harmonised regulatory initiatives create fair and transparent schemes.
- Green economic incentives, as part of public procurement schemes, in pricing and reimbursement systems or as part of pharmacy initiatives and campaigns — these would reward green products and green companies.

The regulatory requirements for the pharmaceutical industry are extensive, particularly with regard to quality and safety; environmental legislative measures are considered by the authorities to be necessary and as an addition to existing pharmaceutical regulations to best balance the risks and benefits of medicines. Voluntary activities can be a relatively fast and flexible way of dealing with the issue, and could provide the public with more information about the risks from concentrations of certain medicines in the environment.⁵³

Research and development, and raw materials

There are ways of designing environmentally benign products and processes to address the environmental issues in the research and development of new medicines.

At the early stage of medicine design and discovery, research work on synthetic organic chemistry is a starting point. There is a growing number of new biological medicines that pose potentially different environmental risks. Medicinal chemists synthesise small amounts (50mg to 1g order) of a large number of medicine candidates for lead optimisation. For example, over 150,000 compounds were synthesised in one year to be

^d This latest manuscript resulted from an EPA internal research grant awarded under the second year of ORD's Pathfinder Innovation Programme: <http://www2.epa.gov/innovation/pathfinder-innovation-projects-awardees-2012>

subjected to initial biological tests (Japanese top 20 pharmaceutical industries data in 2011).⁶⁰ When their biological activity is identified, the selected candidates are further developed through preclinical and clinical stages. In these phases, 10g to 1kg order (preclinical) and 100kg to 1 tonne (clinical) of the candidates are necessary. Only a few of them may finally be approved as new medicines and manufacturers will produce them in large quantities (tonnes). However, more efficient synthetic methods at large scale are expected.

At early developmental stages, quick synthesis of the medicine candidates becomes a high priority, and issues such as the use of expensive and rarely obtained raw materials and toxic or hazardous reagents, high energy consumption (heating or cooling), and generation of chemical waste are often of lesser importance. However, in large-scale applications during preclinical and clinical development, the problems of raw materials, waste, toxicity and energy consumption become more relevant and at this stage the synthetic procedures should be redesigned to maximise efficiency and minimise waste and potential pollution. Metrics such as “atom economy”, “atom efficiency”, “E-factor” and “process mass index” (PMI) can be used in green chemistry to measure the ratio of inputs to outputs in any given product, and determine the overall efficiency of the synthesis (see [Appendix 4](#)). In order to achieve this, process chemistry plays an important role. Typically, process chemists explore many different synthetic pathways to use more renewable raw materials and to reduce (or to eliminate) the generation of waste, the use of energy and hazardous reagents.⁶¹ (Figure 2)

In the mid-1990s Anastas *et al* at the US Environmental Protection Agency (EPA) were developing the concept of “benign by design”, designing environmentally benign products and processes to address the environmental issues of chemical products and processes. This incorporated the concepts of atom economy and E-factor and eventually became a guiding principle of green chemistry as embodied in the 12 Principles of Green Chemistry (see [Appendix 4](#)).⁶²

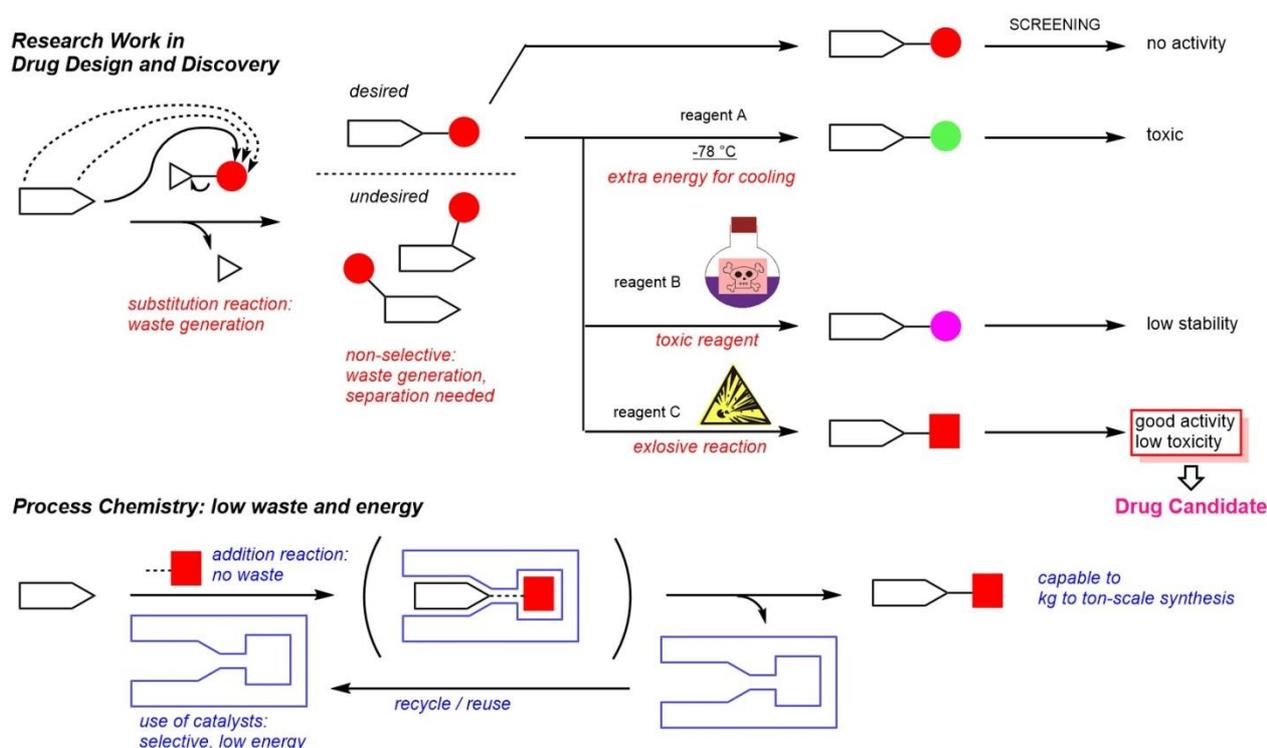
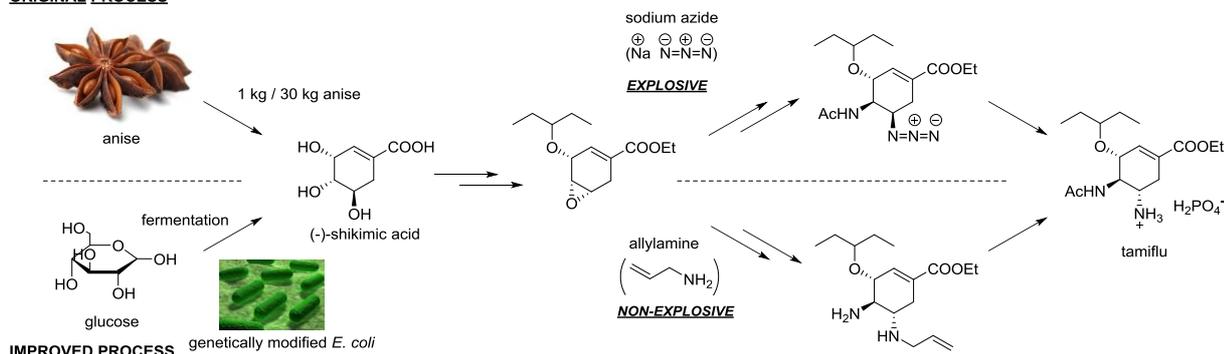


Figure 2: Research and development in drug discovery and the role of process chemistry towards green chemistry⁶³

The development of the anti-influenza medicine oseltamivir phosphate (Tamiflu) is a good example of this process. Oseltamivir phosphate was first synthesised by Gilead and the manufacturing process was developed by Roche. In the first-generation Gilead synthesis, shikimic acid was isolated from Chinese star anise (only 1kg of shikimic acid can be isolated from 30kg of dry anise). They used azide chemistry to introduce the amine group twice. Azide reagents are well known to be explosive. On the other hand, in the second-generation synthesis, Roche scientists developed an alternative process to produce shikimic acid by fermentation. They used a strain of genetically modified *Escherichia coli* as a recombinant microbial biocatalyst to convert renewable raw material glucose to shikimic acid. In addition, they explored an alternative synthetic route with a combination of non-explosive allylamine as a non-azide reagent. Finally, oseltamivir phosphate was obtained in similar reaction steps and total yield (15% yield in 14 reaction steps in the former process, 18% yield in 15 reaction steps

in the latter process) with a significantly reduced risk through the elimination of dangerous and explosive reagents.⁶³(Picture 3)

ORIGINAL PROCESS



Picture 3: Old and improved processes on the manufacture of oseltamivir phosphate (Tamiflu).

Sustainable molecular design of less hazardous molecules

Lessons learnt from designing safer pharmaceuticals provide an outstanding opportunity to design more sustainable industrial chemicals. Several recent studies have applied computational tools to identify attributes of pharmaceuticals during medicine development, and to identify attributes of industrial chemicals presenting increased hazards to aquatic organisms.

Manufacturing and distribution

For decades, “lean” manufacturing operations have been a guiding principle for many industries, including the pharmaceutical industry. Lean is a management philosophy developed by Toyota Production System after World War II. It considers the expenditure of resources used for any goal other than the creation of value to be wasteful, and thus a target for elimination. Lean has dramatically changed the concept of quality. Quality used to be associated strongly with control. Control actions should detect incorrect products before they reach the customer. Lean, on the contrary, focuses on “right first time”. Everyone, and every process, should be an integral part of the product quality. By operators doing things correctly, in the right process sequence, resources are well managed. Lean methodologies and concepts are hence also one way to drive environmentally conscious manufacturing and distribution. Every work practice, process step, energy use, material use, or generation that does not add value should be eliminated. In order to fully describe “green manufacturing and distribution” it is, of course, important to ensure that the operations have the smallest possible environmental impact. Environmental assessments of operations are conducted to identify the ones with high potential environmental burden and those operations should be eliminated if possible, or redesigned to minimise environmental impacts. “Lean & Green” operations are the expected outcome. In addition, the “green chemistry” presented in [Appendix 4](#) under which the industry works diligently to minimise environmental burdens includes, but is not limited to:

Most favoured option

- Prevention of waste
- Minimisation
- Reuse
- Recycling
- Energy recovery
- Disposal



Least favoured option

Companies try to avoid or minimise the use of resources and hence avoid waste generation (Lean & Green). Wherever possible, reuse and recycling efforts are undertaken in order to eliminate the need for disposal of waste. Energy-saving initiatives are run in parallel with efforts to move to renewable energy sources whenever possible.

Packaging materials

Pharmaceutical packages secure the integrity of the medicine within and in some cases help to prevent environmental hazard in the case of breakage. The package should be strong and robust in order to secure patient safety, protect the medicine (from contamination), maximise stability, and ensure ease of storage and transportation. In addition, it should be convenient from a pharmacist's, healthcare professional's and patient's point of view, and is an important carrier of crucial information to all those users. Nevertheless, the selection of packaging designs and materials should also reflect the waste hierarchy described above.

Emission controls

Air emissions from pharmaceutical manufacturing operations could include particulates, volatile organic compounds (VOCs), nitrogen oxides (NO_x), sulphur oxides (SO_x), and carbon dioxide. Several control devices are used to minimise emissions. Their function is either to destroy the contaminants or to remove them from the exhaust stream before it is emitted into the atmosphere.

The current European environmental legislation does not specifically require monitoring and controlling of API emissions. The environmental standards in place are focused on emissions of solvents, particulates and the volatile materials and gases mentioned above. Many international pharmaceutical companies outsource the production of medicines to other countries, e.g. China and India. Evidence exists that some production facilities in these countries discharge considerable amounts of the pharmaceutical production ingredients into the surface water, e.g. antibiotics.²

Production in low income countries contributes to lower prices of medicines in developed countries. However, there are cases where these lower prices have been achieved through environmental negligence. This has led to growing demands on the pharmaceutical industry for reducing the environmental damage caused by their manufacturing processes. In many countries there is a growing awareness, and concern, among consumers and health providers that the manufacturing processes of pharmaceuticals may have a negative impact on the environment. [Appendix 2](#) shows an example of waste management practices from the USA.

Wastewater treatment

Although the industry designs manufacturing processes in order to minimise the generation of waste, it is generally seen as impossible to have "zero emission/discharge operations". Wastewater treatment is the process of removing contaminants from wastewater. It includes biological, physical and chemical processes. Manufacturing plants often use an on-site treatment facility in order to either fully treat the effluent or pre-treat the effluent before it is discharged to an off-site facility, e.g. a publicly owned treatment plant. Generally it can be expected that a treatment plant specifically designed to treat effluent from a pharmaceutical manufacturing plant is more effective in removal of the relevant chemicals than a publicly owned treatment plant that receives both household and industrial effluents. There are several new and advanced wastewater treatment technologies available today, e.g. ozonation together with activated carbon, to increase removal rates of chemical substances of concern.

Third party manufacturers and suppliers

Industry's responsibility for environmental management, as described above, goes well beyond its own fence line to include the global supply chain. Suppliers, especially chemical and biological product suppliers, where environmental impacts could be substantial, must operate effectively and responsibly to safeguard their workers and protect the environment. Pharmaceutical companies should provide relevant support to help suppliers improve their production management skills if necessary. Additionally, it is crucial to evaluate performance of suppliers regularly through onsite audits. The results of such assessments are factored into supplier selection processes. Where improvement is needed, a responsible company supports its suppliers in risk mitigation measures with targeted training and coaching, and requires action plans that call for timely upgrades of facilities and management systems.

Distribution and wholesaling

When considering green distribution and storage, specific areas of focus are CO₂ reductions, improved energy efficiency, minimising disposable wastes, increasing the use of recycled and recyclable materials, and raising

awareness within the involved organisations on the environmental impacts of the businesses, and encouraging dialogue over the ways to reduce them.

Eco-adapted transport and fleet management initiatives

For any business that revolves around large-scale logistics and the transport of a wide variety of products to numerous customers (pharmacies, hospitals, medical facilities, practitioners' offices, and even patients' homes), fleet and transportation management improvements offer great opportunities to reduce carbon dioxide emissions and fuel consumption.

Suppliers are increasingly using energy efficient vehicles for transportation, including electric and hybrid vehicles as well as vehicles that use compressed natural gas rather than traditional gasoline or diesel. In some cases, using compressed natural gas can reduce carbon dioxide emissions by as much as 80%. In addition, suppliers diligently optimise delivery routes to minimise the number of trips required, the distances travelled and the need to frequently revisit the same geographic areas. Drivers are provided with enabling technologies (such as personal digital assistants or global positioning systems) to calculate efficient routes, avoid traffic and minimise delivery times. Some companies also provide vehicle operators with training to promote driving styles and habits that promote greater fuel-efficiency.

Distribution also involves a large volume of packaging and shipping materials, and goods received often must be unwrapped and repackaged in another manner prior to shipment. This packaging may be reusable or for single use. Multiple use packing materials, including items like reusable plastic shipping totes and non-wood pallets, reduce waste. Single use packaging, such as cardboard, is made of recycled materials and is recyclable whenever possible.

Warehousing and storage facility improvement initiatives

In terms of energy efficiency, today's warehouses are increasingly energy efficient through the implementation of light-emitting diode lighting and more efficient refrigeration systems (for cold chain products), heating and air conditioning systems, and information technology systems — thus lowering the consumption of electricity. In addition, the implementation of more innovative technologies and approaches such as solar power, rainwater harvesting and green roof spaces can reduce facilities' carbon footprints by a significant percentage.

A significant proportion of the companies within the international wholesale industry have made these eco-adapted initiatives a core part of their corporate social responsibility programmes and a part of the culture for their employees.

2.3.5 Green offices

Recycling is encouraged across most facilities these days and is promoted through education and awareness activities and supported by processes and programmes that make it easier. Companies are also finding new and efficient ways to reduce paper use both in their warehouse operations and at their corporate offices. For example, recycling bins placed at the desk-side encourage recycling. Whether keeping electronic records, using non-paper communications or implementing electronic ordering and fulfilment systems, new ways of doing the same business in a more environmentally friendly way can be readily achieved. Community pharmacies, too, can regulate their paper, electricity and water usage and can recycle the waste produced.

Confidential patient information is a considerable source of paper waste nowadays and it has to be recycled in a different manner than other medical waste, usually through shredding. Reduction in the use of paper can be achieved by diminishing the amount of photo-copying, and printing of electronic documents, and using only electronic documents whenever possible.

Use of "virtual technology" also helps in the green movement. An office or company that conducts its team meetings via videoconference rather than in person not only eliminates the environmental impacts of travel but also saves time and money in the process, enhancing sustainability.

The key to all successful environmental and conservation programmes is awareness and involvement. If employees (as well as partners) are educated on what the initiatives are and what they may achieve, programmes can be more readily put in place and will enjoy a higher success rate. These types of initiatives also build a sense of teamwork among the staff and within the communities where they maintain operations and serve the public. Direct involvement of employees with Environmental Councils and company-wide celebrations such as "Green Week" are good examples. Employees are encouraged to engage in activities

promoting awareness, and to take action not only within their company, but in their homes and communities as well. These initiatives foster a brighter environmental future for generations to come.^e

2.3.6 Consumers of medicines

Pharmacists are ideally placed to discuss with patients and customers the means for appropriate disposal of unused medicines.

However, in preparation for the practitioner providing relevant information to the patient or consumer at the time a prescription or clinical service is provided, several things need to happen. Some of these prerequisites are political in that they require jurisdictions to recognise the tactical importance of the pharmacists in the resolution of the issue. Some are interprofessional in getting the prescribers to recognise the need to collaborate in the choice of an appropriate medication. And, most of all, the challenge is professional – to add another responsibility to an already burdened practitioner.

Pharmacists are in good position to:

- Provide counselling on the environmental impact and risk of all medicines as an integral part of practice.
- Work together with prescribers (physicians) in choosing medications wisely without jeopardising patient needs and patient safety.
- Access information on environmental risk that is relevant to the medicines available.
Be recognised and accepted by governments and health insurers as key participants in addressing the environmental risk of pharmaceuticals.

FIP supports pharmacists worldwide by collecting and sharing good examples of initiatives and campaigns carried out by pharmacists' organisations worldwide, and links to documents and policies that recognise these issues and provide direction toward their resolution.

For example, a recent document prepared by the Minister of Health, Social Services and Public Safety of Northern Ireland⁶⁴ recognises the value of pharmacists' services in general and specifically the value of pharmacists in the reduction of pharmaceutical waste. The paper specifically looks at issues such as those surrounding adherence and providing prescriptions that are not used, noting that nursing and residential homes are a particular challenge.

A good example of engagement of member organisations with the pharmaceutical industry in their regions to provide information to pharmacists, prescribers and consumers is Stockholm (Sweden) County Council's annually updated publication "Environmentally Classified Pharmaceuticals".⁶⁵ Local professional organisations with assistance from member organisations can provide educational programmes for pharmacists.

It should be possible for pharmacists, physicians, other health care professionals and consumers to access environmental information for pharmaceuticals and specific medicinal products. And, with schemes such as the ones described in the section 1.2.2 Environmental Classification of API of this document, it indeed becomes a possibility for buyers, payers and users of pharmaceuticals to incorporate environmental aspects in their decisions without jeopardising patient needs and patient safety.

Instead of using product-information brochures and leaflets on paper, information sharing via the internet is an example of lowering environmental impacts; it also ensures that existing information is always up to date. Information technology and the use of smart phones and similar devices present promising opportunities for further innovations in minimising environmental impacts. However, such systems are not yet available everywhere.

2.4 Future green pharmacists — education

Future pharmacists must be educated to consider the environmental aspects of medicines use in their practice.

The curriculum for pharmacy education is quite broad and includes:

- Pharmacy technology
- Bio-pharmacy
- Pharmaceutical chemistry
- Pharmacology
- Pharmaceutical biochemistry and pharmacognosy
- Social pharmacy and clinical pharmacy

The pharmacy undergraduate curriculum provides a good basic understanding of medicines metabolism and toxicology which can help to provide an understanding of how medicines and related substances can react in nature and what environmental effects they might have.

Depending on the educational institution and the contents of the curriculum, students may also be informed about green chemistry, environmental issues of medicines development and varying degrees of emphasis about their future role in informing and educating communities, their workplaces and people about the environmental aspects of medicines.

The FIP Education Initiative is a good platform to discuss the role of environmental issues within pharmaceutical education. There are good examples of educational programmes in this field. One example (see [Appendix 4](#)) is given from Åbo Akademi, a Swedish speaking university in Finland preparing BSc level pharmacists. It has organised education in environmental issues as a separate course, where the theoretical knowledge gathered in other courses is brought to this topic. Another possibility is to integrate environmental aspects into every course where appropriate. This change is now under development in the Helsinki University Pharmacy Faculty where the new curriculum will be launched for MSc in Pharmacy studies during 2016. The purpose is to integrate the environmental point of view in all teaching so that the new graduates are able to work according these principles.

References

1. International Pharmaceutical Federation (FIP). Survey on Current Pharmaceutical Waste Management Practices. 2013; The Hague.
2. Larsson DGJ, de Pedro C, Paxeus N. Effluent from drug manufactures contains extremely high levels of pharmaceuticals. *Journal of Hazardous Materials*, 2007; 148(3):751-755.
3. BIO Intelligence Service. Study on the environmental risks of medicinal products, Final Report prepared for Executive Agency for Health and Consumers. 2013.
4. Aud der Beek T, Weber, FA, Bergmann A. (2014). *Results of global database of measured environmental concentrations* [presentation]. Pharmaceuticals in the Environment workshop. Geneva; 2014.
5. Boxall A, Rudd M, Brooks B, Caldwell D, Choi K, Hickmann S et al. Pharmaceuticals and personal care products in the environment: what are the big questions? *Environmental health perspectives*. 2012;120(9):1221-1229.
6. Pettersson I, Berg C. Environmentally relevant concentrations of ethynylestradiol cause female-biased sex ratios in *Xenopus tropicalis* and *Rana temporaria*. *Environmental toxicology and chemistry*. 2007;26(5):1005-1009.
7. Hampel, M., Alonso, E., Aparicio, I., Bron, J. E., Santos, J., L., Taggart, J. B., Leaver, M. J. (2010) Potential physiological effects of pharmaceutical compounds in Atlantic salmon (*Salmo salar*) implied by transcriptomic analysis. *Environ. Sci. Pollut. Res.*, 17, 917-933.
8. Kidd K, Blanchfield P, Mills K, Palace V, Evans R, Lazorchak J et al. Collapse of a fish population after exposure to a synthetic estrogen. *Proceedings of the National Academy of Sciences*. 2007;104(21):8897-8901.
9. Winter, M., J., Lillicrap, A. D., Caunter, J. E., Schaffner, C., Alder, A. C., Ramil, M., Ternes, T. A., Giltrow, E., Sumpter, J. P., Hutchinson, T. H. (2008) Defining the chronic impacts of atenolol on embryo-larval development and reproduction in the fathead minnow (*Pimephales promelas*). *Aquatic Toxicol.*, 86, 361-369.
10. Brodin T, Fick J, Jonsson M, Klaminder J. Dilute concentrations of a psychiatric drug alter behavior of fish from natural populations. *Science*. 2013;339(6121):814-815.
11. Prakash, V., Bishwakarna, M. C., Chaudhary, A., Cuthbert, R., Dave, R., Kulkarni, M., Kumar, S., Paudel, k., Ranade, S., Shringarpure, R., Green, R. E. (2012) The population decline of Gyps Vultures in India and Nepal has slowed since veterinary use of diclofenac was banned. *PloS One*, 7, e-49118.
12. Bengtsson B. Pharmaceuticals, environment and health. Apotheket AB; 2006.
13. Yang, L-H., Ying, G-G., Su, H-C., Stauber, J. L., Adams, M. S., Binet, M. T. (2008) Growth-inhibiting effects of 12 antibacterial agents and their mixtures on the freshwater microalga *Pseudokirchneriella subcapitata*. *Environ. Toxicol. Chem.*, 27(5), 1201-1208.
14. Sehn.org, (2014). *Science & Environmental Health Network - Precautionary Principle*. [online] Available at: <http://www.sehn.org/wing.html> [cited 5 Aug. 2014].
15. Commission of the European Communities. *Communication from the commission on the precautionary principle*. Brussels; 2000. Available from: <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52000DC0001&from=EN>
16. Mattson B. A voluntary environmental classification system for pharmaceutical substances. *Drug information journal*. 2007;41(2):187-191.
17. Fass.se. FASS Allmänhet - Startsidea [Internet]. 2014 [15 July 2014]. Available from: <http://www.fass.se>
18. United States Environmental Protection Agency (EPA). Tox21 [Internet]. Environmental Protection Agency; 2014 [cited 5 Aug. 2014]. Available at: <http://epa.gov/ncct/Tox21>
19. Miller Jr R, Frech III H. Is there a link between pharmaceutical consumption and improved health in OECD countries?. *Pharmacoeconomics*. 2000;18(1):33-45.
20. World Health Organisation (WHO). Global Health and Ageing [Internet]. World Health Organisation; 2011 [15 July 2014]. Available from: http://www.who.int/ageing/publications/global_health.pdf
21. Farrell B, Szeto W, Shamji S. Drug-related problems in the frail elderly. *Canadian Family Physician*. 2011;57(2):168-169.
22. United Nations. World Population Prospects: The 2012 Revision [Internet]. Department of Economic and Social Affairs. 2014 [15 July 2014]. Available from: <http://esa.un.org/unpd/wpp/index.htm>
23. World Health Organization (WHO). Urban Population Health [Internet]. 2014. Available from: http://www.who.int/gho/urban_health/situation_trends/urban_population_growth_text/en/

24. Centers for Disease Control and Prevention. Prescription Drug Overdoses: An American Epidemic [Internet]. 2014 [15 July 2014]. Available from: <http://www.cdc.gov/about/grand-rounds/archives/2011/01-February.html>
25. Woolf M. Residual medicines: a report on OPCS Omnibus Survey data. University of London; 2010.
26. Brooks B, Riley T, Taylor R. Water quality of effluent-dominated ecosystems: ecotoxicological, hydrological, and management considerations. *Hydrobiologia*. 2006;556(1):365-379.
27. Brooks B. Fish on Prozac (and Zoloft): Ten years later. *Aquatic Toxicology*. 2014;151:61-67.
28. National Research Council. Water Reuse: Potential for Expanding the Nation's Water Supply Through Reuse of Municipal Wastewater. Washington, DC: The National Academies Press, 2012.
29. UN Informal Interagency Joint Programme Proposal: Greening Procurement in the Health Sector. 2013. Available from: http://apps.who.int/prequal/trainingresources/pq_pres/meeting_WHO_UNICEF_UNFPA_2013/Day_2/29_Singh-Sorensen.pdf
30. World Health Organisation (WHO). Greening health systems [meeting report]. Copenhagen: World Health Organisation; 2013.
31. World Health Organisation (WHO). Health and Environment in Sustainable Development: Five Years after the Earth Summit. Geneva: World Health Organisation; 1997
32. Smith K, Corvalán C, Kjellstrom T, others. How much global ill health is attributable to environmental factors?. *Epidemiology-Baltimore*. 1999;10(5):573-584.
33. World Health Organisation (WHO). Health and Environment Linkages Initiative [Internet]. 2014 [15 July 2014]. Available from: <http://www.who.int/heli/en/>
34. World Health Organisation (WHO) Regional Office for Africa. Environmental Health Policies [Internet]. 2014 [15 July 2014]. Available from: <http://www.afro.who.int/en/clusters-a-programmes/hpr/protection-of-the-human-environment/programme-components/environmental-health-policies.html>
35. Living well, within the limits of our planet. 7th EAP: The new general Union Environment Action Programme to 2020. Luxembourg, 2014. ISBN 978-92-79-34724-5
36. Factsheet on living well, within the limits of our planet. 7th EAP: The new general Union Environment Action Programme to 2020. Luxembourg, 2014. [6 November 2014]. Available from: <http://ec.europa.eu/environment/newprg/index.htm>
37. Swedish Environmental Management Council (SEMCO) [Internet]. 2014 [cited 5 August 2014]. Available from: <http://www.msr.se/en/>
38. Centers for Disease Control and Prevention (CDC). HAZARDOUS DRUG EXPOSURES IN HEALTH CARE [Internet]. 2013 [15 July 2014]. Available from: <http://www.cdc.gov/niosh/topics/hazdrug/>
39. U.S. Pharmacopeial Convention. General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings | U.S. Pharmacopeial Convention [Internet]. 2014 [15 July 2014]. Available from: <http://www.usp.org/usp-nf/notices/compounding-notice>
40. Joint FIP/WHO guidelines on good pharmacy practice: standards for quality of pharmacy services. WHO Technical Report Series, No. 961, 2011. Geneva: World Health Organization, 2011 http://www.fip.org/files/fip/WHO/GPP%20guidelines%20FIP%20publication_final.pdf
41. Daughton C. Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. I. Rationale for and avenues toward a green pharmacy. *Environmental Health Perspectives*. 2003;111(5):757.
42. European Commission. Eco-Management and Audit Scheme (EMAS) [Internet]. 2014 [15 July 2014]. Available from: http://ec.europa.eu/environment/emas/index_en.htm
43. Butler C, Rollnick S, Pill R, Maggs-Rapport F, Stott N. Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats. *Bmj*. 1998;317(7159):637-642.
44. Kallestrup P, Bro F. Parents' beliefs and expectations when presenting with a febrile child at an out-of-hours general practice clinic. *British journal of general practice*. 2003;53(486):43-44.
45. Macfarlane J, Holmes W, Macfarlane R, Britten N. Influence of patients' expectations on antibiotic management of acute lower respiratory tract illness in general practice: questionnaire study. *Bmj*. 1997;315(7117):1211-1214.
46. Rutten G, Van Eijk J, Beek M, Van der Velden H. Patient education about cough: effect on the consulting behaviour of general practice patients. *British Journal of General Practice*. 1991;41(348):289-292.

47. Kümmerer K. The presence of pharmaceuticals in the environment due to human use--present knowledge and future challenges. *Journal of environmental management*. 2009;90(8):2354-2366.
48. European Environmental Agency (EEA). *Pharmaceuticals in the environment: results of an EEA workshop*. Copenhagen: European Environmental Agency; 2010. ISBN 978-92-9213-063-3
49. Académie nationale de Pharmacie. *MÉDICAMENTS ET ENVIRONNEMENT*. Paris: Académie nationale de Pharmacie; 2008.
50. Ordre national des médecins. *La prescription et la place du médicament dans la relation Médecin-Patient-Pharmacien. Aspects réglementaires, éthiques et déontologiques*. Commission Nationale Permanente 2011-2012; 2012.
51. EU Directive 2001/83/, Article 127b, Community code relating to medicinal products for human use, as amended, can be found here: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_cons2009/2001_83_cons2009_en.pdf
52. Académie nationale de Pharmacie. *MÉDICAMENTS ET ENVIRONNEMENT*. Paris: Académie nationale de Pharmacie; 2008.
53. European Environmental Agency (EEA). *Pharmaceuticals in the environment: results of an EEA workshop*. Copenhagen: European Environmental Agency; 2010.
54. CYCLAMED [Internet]. 2014 [15 July 2014]. Available from: <http://www.cyclamed.org/>
55. SIGRE [Internet]. 2013 [15 July 2014]. Available from: <http://www.sigre.es/>
56. Valormed [Internet]. 2014 [15 July 2014]. Available from: <http://www.valormed.pt>
57. The National Return & Disposal of Unwanted Medicines. *Return Unwanted Medicines | The RUM Project* [Internet]. 2011 [15 July 2014]. Available from: <http://www.returnmed.com.au/>
58. International Pharmaceutical Federation (FIP). *POPAD* [Internal Database]. 2014; The Hague.
59. Daughton C, Ruhoy I. Lower-dose prescribing: minimizing “side effects” of pharmaceuticals on society and the environment. *Science of the Total Environment*. 2013;443:324-337.
60. Japan Pharmaceutical Manufacturers Association. *Data Book*. 2013; pp 46.
61. Dunn P, Wells A, Williams M. *Green chemistry in the pharmaceutical industry*. Chapter 1. 1st ed. Weinheim: Wiley-VCH; 2010.
62. Anastas, P. T. and Warner, J. C. *Green Chemistry: Theory and Practice*. Oxford University Press: New York, 1998, p. 30.
63. Van Koevering J. *The Challenges of Tamiflu Manufacture* [Internet]. 1st ed. Roche; 2014 [15 July 2014]. Available from: http://www.roche.com/med_mb091105jvk.pdf
64. Department of Health, Social Services and Public Safety, Northern Ireland. *Making it Better through Pharmacy in the Community – a Five Year Strategy for Pharmacy in the Community*. 2014.
65. *ENVIRONMENTALLY CLASSIFIED PHARMACEUTICALS*. 1st ed. Stockholm: Miljemarket Trycksak Lic; 2012. Available from: <http://www.pharmaenvironment.org/en/resources/environmentally-classified-pharmaceuticals-2012-35>

Further reading

- Loos R, Carvalho R, Comero S, et al. EU Wide Monitoring Survey on Waste Water Treatment Plant Effluents [Internet]. 1st ed. European Commission Joint Research Centre Institute for Environment and Sustainability; 2012 [15 July 2014]. Available from: <http://publications.jrc.ec.europa.eu/repository/bitstream/111111111/26927/1/lb-na-25563-en.pdf.pdf>
- Gilbert N. Drug-pollution law all washed up. *Nature*. 2012;491(7425):503-504.
- Svensson J, Fick J, Brandt I, Brunström B. The synthetic progestin levonorgestrel is a potent androgen in the three-spined stickleback (*Gasterosteus aculeatus*). *Environmental science & technology*. 2013;47(4):2043-2051.
- Fick J, Lindberg R, Parkkonen J, Arvidsson B, Tysklind M, Larsson D. Therapeutic levels of levonorgestrel detected in blood plasma of fish: results from screening rainbow trout exposed to treated sewage effluents. *Environmental science & technology*. 2010;44(7):2661-2666.
- Gyllenhammar I, Holm L, Eklund R, Berg C. Reproductive toxicity in *Xenopus tropicalis* after developmental exposure to environmental concentrations of ethynylestradiol. *Aquatic Toxicology*. 2009;91(2):171-178.
- Säfholm M, Norder A, Fick J, Berg C. Disrupted oogenesis in the frog *Xenopus tropicalis* after exposure to environmental progestin concentrations. *Biology of reproduction*. 2012;86(4):126.
- Zeilinger J, Steger-Hartmann T, Maser E, Goller S, Vonk R, Lange R. Effects of synthetic gestagens on fish reproduction. *Environmental Toxicology and Chemistry*. 2009;28(12):2663-2670.
- Gilbert N. Drug waste harms fish. *Nature*. 2011;476(7360):265.
- Owen R, Jobling S. Environmental science: The hidden costs of flexible fertility. *Nature*. 2012;485(7399):441-441.
- Berg C, Backström T, Winberg S, Lindberg R, Brandt I. Developmental exposure to fluoxetine modulates the serotonin system in hypothalamus. *PloS one*. 2013;8(1):55053.
- Valenti Jr T, Gould G, Berninger J, Connors K, Keele N, Prosser K et al. Human therapeutic plasma levels of the selective serotonin reuptake inhibitor (SSRI) sertraline decrease serotonin reuptake transporter binding and shelter-seeking behavior in adult male fathead minnows. *Environmental science & technology*. 2012;46(4):2427-2435.
- Finley R, Collignon P, Larsson D, McEwen S, Li X, Gaze W et al. The scourge of antibiotic resistance: the important role of the environment. *Clinical infectious diseases*. 2013;355.
- Pruden A, Larsson D, Amézquita A, Collignon P, Brandt K, Graham D et al. Management options for reducing the release of antibiotics and antibiotic resistance genes to the environment. *Environ Health Perspect*. 2013;121(8):878-885.
- Woolf M. Residual medicines: a report on OPCS Omnibus Survey data. University of London; 2010.
- York Health Economics Consortium, School of Pharmacy University of London. Evaluation of the Scale, Causes and Costs of Waste Medicines. London: YHEC/School of Pharmacy, University of London; 2010.
- Oldenkamp R, Huijbregts M, Hollander A, Versporten A, Goossens H, Ragas A. Spatially explicit prioritization of human antibiotics and antineoplastics in Europe. *Environment international*. 2013;51:13-26.
- Hughes S, Kay P, Brown L. Global synthesis and critical evaluation of pharmaceutical data sets collected from river systems. *Environmental science & technology*. 2012;47(2):661-677.
- Fick J, Söderström H, Lindberg R, Phan C, Tysklind M, Larsson D. Contamination of surface, ground, and drinking water from pharmaceutical production. *Environmental Toxicology and Chemistry*. 2009;28(12):2522-2527.
- ter Laak T, van der Aa M, Houtman C, Stoks P, van Wezel A. Relating environmental concentrations of pharmaceuticals to consumption: a mass balance approach for the river Rhine. *Environment international*. 2010;36(5):403-409.
- Zuccato E, Castiglioni S, Fanelli R. Identification of the pharmaceuticals for human use contaminating the Italian aquatic environment. *Journal of Hazardous Materials*. 2005;122(3):205-209.
- Segura P, François M, Gagnon C, Sauvé S, et al. Review of the occurrence of anti-infectives in contaminated wastewaters and natural and drinking waters. *Environ Health Perspect*. 2009;117(5):675-684.
- Touraud E. Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters [Internet]. 1st ed. Paris: ARMINES - Ecole des Mines d'Alès; 2008 [15 July 2014]. Available from: http://environmentalhealthcollaborative.org/images/KNAPPE_REPORT_FINAL.pdf

23. Loos R, Carvalho R, Antonio D, Comero S, Locoro G, Tavazzi S et al. EU-wide monitoring survey on emerging polar organic contaminants in wastewater treatment plant effluents. *Water research*. 2013;47(17):6475-6487.
24. French Agency for Food, Environmental and Occupational Health & Safety (ANSES). National analysis campaign on drug residues in water: results in line with expectations | ANSES - Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail [Internet]. 2011 [15 July 2014]. Available from: <https://www.anses.fr/en/content/national-analysis-campaign-drug-residues-water-results-line-expectations>
25. Vulliet E, Cren-Olivé C, Grenier-Loustalot M. Occurrence of pharmaceuticals and hormones in drinking water treated from surface waters. *Environmental Chemistry Letters*. 2011;9(1):103-114.
26. Mompelat S, Le Bot B, Thomas O. Occurrence and fate of pharmaceutical products and by-products, from resource to drinking water. *Environment international*. 2009;35(5):803-814.
27. Touraud E, Roig B, Sumpter J, Coetsier C. Drug residues and endocrine disruptors in drinking water: risk for humans?. *International journal of hygiene and environmental health*. 2011;214(6):437-441.
28. CELESIO. Environment [Internet]. 2014 [15 July 2014]. Available from: http://www.celesio.com/en/CR/Our_responsibility/Environment/
29. Alliance Boots. Our environment target highlights [Internet]. 2013 [15 July 2014]. Available from: <http://www.allianceboots.com/csr-initiatives/our-environment-target-highlights.aspx>
30. Suzuken Co. Corporate Social Responsibility [Internet]. 2014 [15 July 2014]. Available from: <http://www.suzuken.co.jp/english/whats/responsible.html>
31. UDG Healthcare plc. Corporate Social Responsibility (CSR) [Internet]. 2014 [15 July 2014]. Available from: <http://www.udghealthcare.com/about/corporate-social-responsibility/>
32. McKesson. Environmental Sustainability [Internet]. 2014 [15 July 2014]. Available from: <http://www.mckesson.com/about-mckesson/corporate-citizenship/environmental-sustainability/>
33. MEDIQ. Beperken schadelijke gevolgen voor milieu [Internet]. 2014 [15 July 2014]. Available from: <http://www.mediq.com/nl-nl/mvo/het-beperken-van-schadelijke-gevolgen-voor-het-milieu.aspx>

Appendices

- Appendix 1: Examples of environmental policies and practices in hospital pharmacies
- Appendix 2: Pharmaceutical waste management and disposal practices — an example from the USA
- Appendix 3: Example of information for customers about an unused medicines collection programme
- Appendix 4: Green chemistry
- Appendix 5: Medicines and the Environment academic course at Åbo Akademi, Finland
- Appendix 6: Disaster management

Appendix 1. Examples of environmental policies and practices in hospital pharmacies

The Hospital District of Helsinki and Uusimaa (HUS) is a joint authority formed by 24 municipalities in Southern Finland. It aims to offer patients in all member municipalities timely and equal access to specialised medical care. The municipal federation owns and runs HUS pharmacy, which takes care of all pharmacy activities in every hospital in the district.

The district has developed its own environmental policy which is coordinated by HUS-environmental centre. There is an environment committee on which the pharmacy is represented. In every unit of the pharmacy there is a pharmacist who is educated in environmental issues and is responsible for the actions in that unit. Together these units form the pharmacy environmental committee, which meets twice a year to discuss policy and actions. A medical waste collection programme is running in every hospital. This is the responsibility of the pharmacy. All clinics must follow a standard operating procedure on medical waste.⁶⁶

Appendix 2. Pharmaceutical waste management and disposal practices — an example from the USA

Appropriate management of pharmaceutical waste is now recognised as a public health concern due to increasing evidence of APIs in surface, ground and drinking waters. Pharmaceutical waste includes expired, unused, spilt and contaminated pharmaceutical products, vaccines and sera that are no longer required, and, due to their chemical or biological nature, need to be disposed of carefully. The category also includes discarded items heavily contaminated during the handling of pharmaceuticals, such as bottles, vials and boxes containing pharmaceutical residues, gloves, masks and connecting tubing.⁶⁶

Genotoxic waste also falls under pharmaceutical waste. It is highly hazardous and may have mutagenic, teratogenic, or carcinogenic properties. Cytotoxic drugs are the principal substances in this category, together with vomit, urine or faeces from patients treated with cytostatic drugs, chemicals and radioactive material. The disposal of genotoxic waste raises serious safety problems, both inside hospitals and after disposal, and should be given special attention.⁶⁶

The waste produced in the course of health care activities, from contaminated needles to radioactive isotopes, carries a greater potential for causing infection and injury than any other type of waste, and inadequate or inappropriate management is likely to have serious public health consequences and deleterious effects on the environment.⁶⁶

Applying the safest method of pharmaceutical waste disposal, based on the WHO Guidelines, should be a top priority for pharmacists and the communities and countries in which they practise in parallel with reducing pharmaceutical waste through a variety of methods, including better inventory control, appropriate prescribing and increased patient compliance.

A2.1 Pathways by which pharmaceuticals become waste

To understand and manage the problem, we need to first look at the environmental impact across the whole life cycle of pharmaceuticals during their production, consumption and disposal.

⁶⁶ More information about the work can be found in the following link: [www.hus.fi/annual report 2012](http://www.hus.fi/annual%20report%202012), pages 38-39 where the environmental policy of the district is described.

There are four distinct ways by which pharmaceutical waste is generated:

- I. At the point of care, such as hospitals and clinics,
- II. From undispensed or unused pharmaceuticals,
- III. By consumers, either through use of medicines or disposal of unused medicines
- IV. During the manufacturing and distribution process.

The increasing consumption of medicines makes the problem of pharmaceutical waste more difficult to manage.

A2.2 Waste management according to the pathways by which pharmaceuticals become waste — the USA perspective

Waste management of pharmaceuticals generated at the point of care

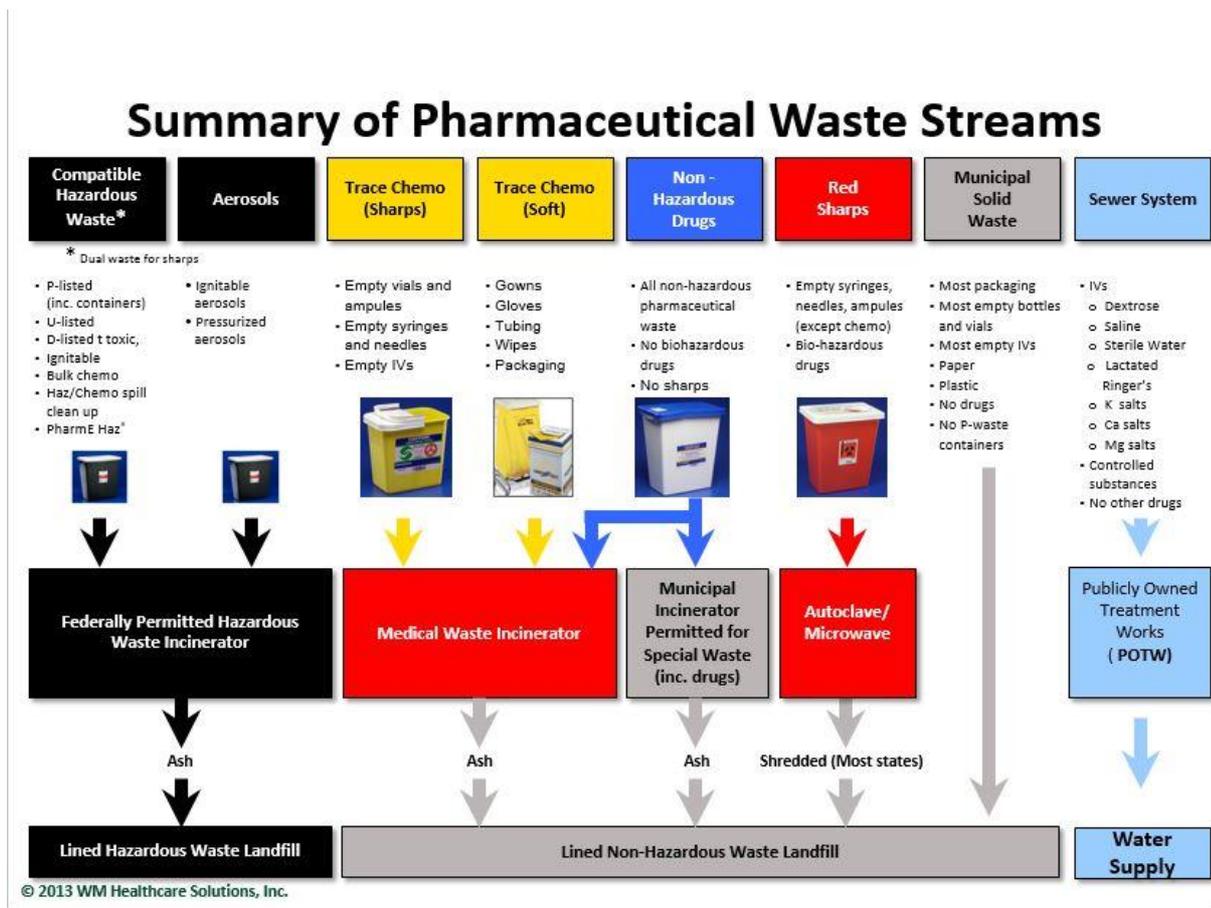
Of the different steps of a medicine's life-cycle, the consumption stage is the most important contributor to the release of medicinal products into the environment.⁶⁷ A study (Lienert, 2007) analysed the excretion pathways of 212 human APIs, equalling 1,409 products. On average, 64% (+/- 27%) of each API was excreted in the urine, and 35% (+/- 26%) in the faeces. However, the quality and quantity of excreted molecules and metabolites is highly variable. For example, 80–90 % of amoxicillin is released in its original form, whereas only 3% of carbamazepine is released unchanged.⁶⁸ Excretions by patients undergo wastewater treatment, which is often inadequate.⁶⁹

Also, portions of dermally applied pharmaceuticals, such as gels containing anti-inflammatories, may be washed off the skin during showering or bathing (and will undergo wastewater treatment). For example, only 2% of a dermal dose of pyrethrums is absorbed and metabolised.⁷⁰

Where wastewater infrastructure exists, the excreted medicines will be collected in wastewater treatment plants (WWTPs) for treatment. The main task of WWTPs is to remove biological waste from water but not APIs and other chemical substances. Therefore, certain APIs are not removed but are discharged into surface waters or aquifers, which may then be recycled into the water supply. During the treatment, some of the APIs may undergo a primary degradation and form toxic metabolites. Increasingly, resources are being invested in the development of more effective cleaning techniques. Removal of APIs at the WWTPs requires a number of methods to be employed, many of which are expensive.

Managing medicines that become waste at health care facilities is a significant challenge because of the complexity of the environment, which is focused on patient care. Over the past 10 years in the USA, hospitals have come under greater scrutiny by the US Environmental Protection Agency (EPA) and state environmental authorities. The EPA enforces the Resource Conservation and Recovery Act (RCRA), passed in 1976, which defines hazardous chemical waste and requires cradle-to-grave tracking and disposal at a permitted hazardous waste incinerator. About 5% of the medicines in the US market become a RCRA hazardous waste when disposed of. Since the law has never been updated, another 8% to 10% of medicines should be managed in this manner based on their toxicity. Approximately 60% of hospitals in the USA are managing hazardous pharmaceutical waste “cradle to grave,” up from 18% in 2008.⁷¹ Several states prohibit flushing of medicines down the drain, but this is still a common practice in many health care facilities. In addition, any materials that have come into contact with chemotherapy products, commonly called “trace chemotherapy,” are routinely segregated for incineration at a regulated medical waste incinerator. *Table 2*, below, describes a typical waste segregation scheme.

Table 2: Summary of Pharmaceutical Waste Streams



This summary assumes the availability of (a) hazardous waste incinerators, permitted to accept those medicines designated as hazardous waste, (b) regulated medical waste incinerators and (c) waste-to-energy incinerators, many of which are permitted to incinerate non-hazardous pharmaceutical waste. The ash from these incinerators is then delivered to hazardous or non-hazardous waste landfills, depending on the original waste stream. Cement kilns are used in some cases for both hazardous and non-hazardous pharmaceutical waste destruction, based on their permits. The trace chemotherapy waste is routinely incinerated at a regulated medical waste incinerator, along with pathology waste. Since not all of these options are available outside the USA, additional options will be discussed shortly.

The indiscriminate and erratic handling and disposal of pharmaceutical waste within health care facilities is now widely recognised as a source of avoidable environmental contamination, and is synonymous with public perception of poor standards of health care.

Prompted by the Unused Pharmaceutical Safe Disposal Act in the District of Columbia, health care providers in the USA have rolled out a series of pharmaceutical disposal methodologies to avoid disposal in the wastewater. This involves the use of coloured bins and Smart Sinks. These methodologies are presently being rolled out at hospitals in Washington, D.C. and Maryland as a best practice. The waste streams which have been set up are summarised and different waste vendors have been engaged to handle each pharmaceutical waste category. (Table 3)

Table 3: Example of handling different pharmaceutical waste categories

Type of Waste	Sharps (Red Sharps Container)	Trace Chemo and Combined Chemo/Infectious HD High/Low (Yellow Bucket)	Chemo and EPA Regulated (Black Bucket)	Controlled Substance (CS) Non-hazardous, non-EPA Fentanyl patches (Green Smart Sink system)	Specific Exempted Solutions listed below Containing NO medications (Sink Drain or Toilet)	All OTHER Pharmaceutical Waste (Blue Bucket)	Infectious Waste (Red bucket with bag)	Ordinary Trash (White bucket with a clear bag)
Description of Waste	<ul style="list-style-type: none"> all sharp objects that have not been exposed to chemo lancets needles/syringes scalpels scissors broken glass/vials specimen containers (blood) - glass 	<ul style="list-style-type: none"> EMPTY chemo containers (IV bags, tubing, vials, syringes, zip lock bags). <ul style="list-style-type: none"> EMPTY - Less than 3% of the contents remain IV sets that have held chemo and remain attached to catheter or other bloody material Gloves, gowns, Ziploc bags, other paraphernalia used to administer chemo but NOT VISIBLY CONTAMINATED with chemo (i.e. no known droplet or spill) Chemo sharps MedStar designated HD High and low drugs 	<ul style="list-style-type: none"> NOT EMPTY chemo bags/syringes/vials that have NO CATHETER attached Paraphernalia (e.g. gloves, gowns) VISIBLY CONTAMINATED with specified chemo. <ul style="list-style-type: none"> Materials used to clear clean up of specified chemo spill (BAGGED) Non-chemo EPA Regulated (marked with small rectangular black sticker with white letters reading "EPA," or small solid black rectangle adjacent to drug name for some unit dosed items) for example: <ul style="list-style-type: none"> Nicotine Patches Warfarin (tablet & unit dose packaging) Insulin vials <p>Contact pharmacy for more info *** NO NEEDLES ***</p>	<ul style="list-style-type: none"> Status: <ul style="list-style-type: none"> Maryland Sites - to be installed FY15; continue to follow current practice DC Sites - in place Contains 2 canisters; one each for raw solid and liquid CS waste, patch slot Liquid waste from CS syringes or vials should be expressed into the container Do not insert syringes or vials Renderers solid and liquid pharmaceutical waste unrecoverable and unusable Filled canisters are picked up by the Safety Department 	<ul style="list-style-type: none"> Sterile Water Dextrose solutions (such as D5W) Saline solutions (such as 0.9% NaCl) Lactated Ringers Potassium salts (such as potassium chloride) Calcium salts (such as calcium chloride and calcium gluconate) Magnesium salts (such as magnesium sulfate) 	<ul style="list-style-type: none"> Status: <ul style="list-style-type: none"> Maryland Sites - to be installed FY15; continue to follow current practice DC Sites and MSMH - in place No "EPA" stickered drug waste No controlled substances No NEEDLES/sharps No infectious waste No chemo waste No trash 11 gal. capacity 	<ul style="list-style-type: none"> Materials not exposed to chemo but saturated with blood or bodily fluids (i.e. could get a drop out by squeezing or flicking) Containers of blood products or other potentially infectious materials. <p><i>Absorbent materials not saturated with blood or bodily fluids should be disposed of as ordinary trash.</i></p>	<ul style="list-style-type: none"> Materials not exposed to chemo and not saturated with blood or bodily fluids (i.e. could not get a drop out by squeezing or flicking). <p>Examples:</p> <ul style="list-style-type: none"> Non-chemo IV bags Packaging Food Waste
Disposal Method	Ground, microwaved and landfilled, container is cleaned and reused.	Sent to medical waste incinerator.	Sent to hazardous waste incinerator.	Picked up by pharmaceutical reverse vendor.	On site sink drain or toilet.	Sent to medical waste incinerator.	1. Autoclaved on premises and sent to landfill, or 2. Sent to an offsite medical waste incinerator.	Sent to municipal landfill.

A Florida hospital is starting a Multi-Dose Medication Dispensing at Discharge Programme to minimise waste of inhalers and other multi-dose pharmaceuticals. Currently Florida law prohibits a partially used metered-dose inhaler or eye drop container from being sent home with a patient. This results in many such containers being discarded every day from this 1,500-bed hospital. The hospital has received a waiver to the law that allows it to send the partially used container home with the patient for continued use. This has a positive impact on waste discharge as well as saving money for the hospital and the patient.⁷

The WHO developed its Blue book⁷² to provide comprehensive guidance on safe, efficient and environmentally sound methods for the handling and disposal of pharmaceutical waste in normal situations and emergencies. Future issues such as climate change and the changing patterns of diseases and their impacts on health care waste management are also discussed, as well as guiding regulatory principles for developing local or national approaches to tackling pharmaceutical waste management and transposing these into practical plans for regions and individual health care facilities. Specific methods and technologies are described for waste minimisation, segregation and treatment of pharmaceutical waste.

Waste management of undispensed, outdated pharmaceuticals

Regulatory bodies throughout the world require manufacturers to do stability testing to determine a reasonable shelf life for products, assuming room temperature, or in the case of some medicines, refrigerated storage. A percentage of medicines, usually around 2%, will expire on pharmacy shelves before they can be dispensed. In the USA, a system of reverse logistics has been developed that assures many of these medicines will be properly managed and disposed of at either a hazardous waste incinerator or a waste-to-energy incinerator. In many cases, credit is offered by the manufacturer if certain documentation protocols are followed. Most hospital and community pharmacies in the USA utilise this reverse distribution procedure.⁸ A pharmaceutical reverse-distribution industry has been active in the USA since the early 1990s, facilitating such practices and generally providing appropriate disposal. Disposal is by incineration based on the designations noted in the pharmaceutical waste chart, minus regulated medical waste.

Waste management of pharmaceutical waste generated by consumers

The collection and proper disposal of unwanted consumer medicines in the USA lags behind schemes currently available in Canada, Australia and some EU countries. Two primary barriers exist: current Drug Enforcement

⁷ Health system in Florida, USA

⁸ The USA 1976 Resource Conservation and Recovery Act (RCRA) is the principal federal law in the US governing the disposal of solid waste and hazardous waste (Resource Conservation and Recovery Act, P.L. 94-580, 90 Stat. 2795, 42 U.S.C. § 6901 et seq., October 21, 1976). The Federal list of Hazardous Drug Exposures in Health Care focuses on employee safety (<http://www.cdc.gov/niosh/topics/hazdrug/>). Standards are currently being written for Hazardous Drugs—Handling in Healthcare Settings (<http://www.usp.org/usp-nf/notices/compounding-notice>).

Administration (DEA) regulations, which prohibit the return of a controlled substance to anyone but law enforcement, and no stable mechanism for funding such programmes. The first barrier has been addressed with the passage of the Safe and Responsible Drug Disposal Act of 2010, which directs the USA Attorney General, through the DEA, to generate revised regulations enabling more options. These proposed regulations were published on 21 December 2012 for a 60-day comment period. The final regulations were published on 9 September 2014.⁹ With respect to the funding aspects, support from the pharmaceutical industry has been sought vigorously but has not yet materialised to any great extent. With respect to disposal options, due to a household hazardous waste exemption federally and in many states, consumer-generated pharmaceuticals can often be incinerated at waste-to-energy facilities but are also treated at hazardous waste incinerators.

Waste management of pharmaceuticals generated during the manufacturing and distribution process

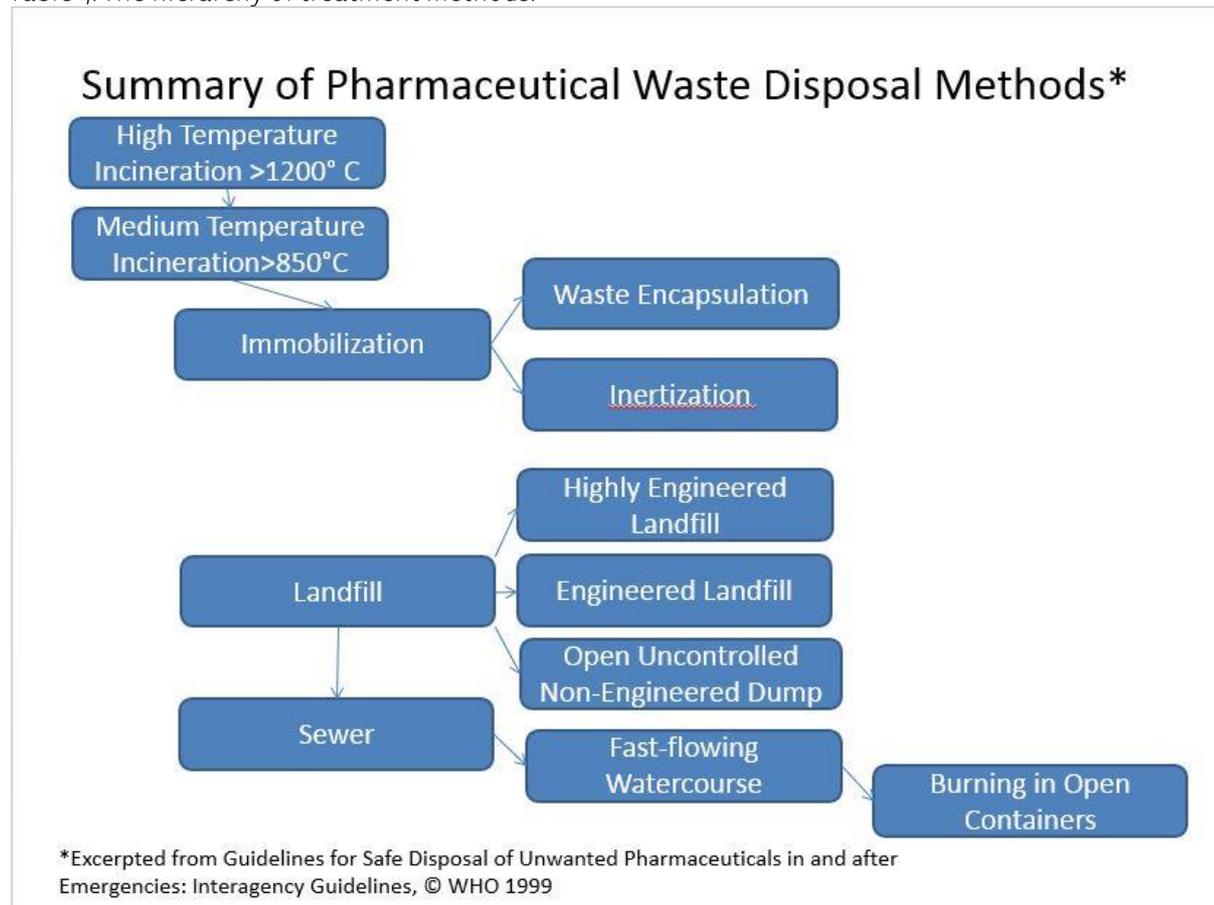
Refer to the part 2.3.3 of the main document.

A2.3 Methods of treatment and disposal: A hierarchy of treatment

The WHO delineated a hierarchy of treatment methods as early as 1999,⁷³ and this has been adopted by Ethiopia,⁷⁴ Tanzania,⁷⁵ and other countries. Although the initial purpose of the guidelines was to deal with large quantities of medicines donated during emergencies, the methods are sound and offer alternatives to incineration in countries and areas that do not have ready access to incineration facilities. Moving disposal methods to the upper half of the hierarchy is a worthwhile goal. Disposal via the sewer and open burning should be eliminated whenever possible.

The hierarchy is as follows in *Table 4* below.

Table 4: The hierarchy of treatment methods.



References

⁹ Regulations to the Safe and Responsible Drug Disposal Act of 2010. Available here: http://www.deadiversion.usdoj.gov/drug_disposal/

66. World Health Organisation (WHO). Safe management of wastes from health-care activities. 2nd ed. Geneva: World Health Organisation; 2014 [15 July 2014]. Available from: http://www.who.int/water_sanitation_health/medicalwaste/wastemanag/en/
67. Bound J, Voulvoulis N. Household disposal of pharmaceuticals as a pathway for aquatic contamination in the United Kingdom. *Environmental health perspectives*. 2005;113:1705-1711.
68. Lienert J, Burki T, Escher B. Reducing micropollutants with source control: substance flow analysis of 212 pharmaceuticals in faeces and urine. *Water Science & Technology*. 2007;56(5):87-96.
69. Schwarzenbach R, Escher B, Fenner K, Hofstetter T, Johnson C, Von Gunten U et al. The challenge of micropollutants in aquatic systems. *Science*. 2006;313(5790):1072-1077.
70. Boxall A, Kolpin D, Halling-Sørensen B, Tolls J. Are veterinary pharmaceuticals causing environmental risks? *Environ Sci Technol*. 2003;37(15):286A-294A.
71. Pharmacy Purchasing & Products. "Going Green" [Internet]. 2013 [15 July 2014]; Available from: <http://pppmag.com/digitalmag/Main.php?MagID=4&MagNo=103>
72. World Health Organisation (WHO). Safe management of wastes from health-care activities. 2nd ed. Geneva: World Health Organisation WHO; 2014. Available from: http://apps.who.int/iris/bitstream/10665/85349/1/9789241548564_eng.pdf
73. World Health Organisation (WHO). Guidelines for Safe Disposal of Unwanted Pharmaceuticals in and after Emergencies: Interagency Guidelines. World Health Organisation; 2014 [15 July 2014] Available from: http://www.who.int/water_sanitation_health/medicalwaste/unwantpharm.pdf
74. Ejigu E, Tadeg H, Mekonnen N. Establishment of Medicines Waste Management and Disposal System in Ethiopia: a Report on Progress and Achievements. 1st ed. Arlington: Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program; 2012 [15 July 2014]. Available from: <http://siapsprogram.org/wp-content/uploads/2013/01/13-093-MedicinesWasteDisposal-Ethiopia-FINAL.pdf>
75. Tanzania Food and Drugs Authority (TFDA). Guidelines for Safe Disposal of Unfit Medicines and Cosmetic Products. Tanzania Food and Drugs Authority (TFDA); 2009.

Further reading

34. Lauer L. RCRA and Pharmaceutical Waste Management: A Brief Federal Overview. 2010 [15 July 2014]. Available from: <http://www.deq.state.ok.us/lpdnew/HW/PharmaceuticalWaste/RCRAAndPharmaceuticalWasteMan.pdf>
35. Smith, C. Managing Pharmaceutical Waste: A 10-Step Blueprint for Healthcare Facilities in the United States [Internet]. 2nd ed. PRACTICE GreenHealth; Rev 2008 [15 July 2014]. Available from: <http://www.hercenter.org/hazmat/tenstepblueprint.pdf>
36. Smith C. Managing Pharmaceutical Waste: What Pharmacists Should Know. *Journal of the Pharmacy Society of Wisconsin*. 2002 [15 July 2014]. Available from: http://www.ashp.org/s_ashp/docs/files/PSW_article.pdf
37. Illinois-Indiana Sea Grant. Disposal of Unwanted Medicines: A Resource for Action in Your Community [Internet]. 1st ed. Indiana: Illinois-Indiana Sea Grant; 2014 [15 July 2014]. Available from: <http://www.seagrant.sunysb.edu/Images/Uploads/PDFs/RUMDoseofReality-UnwantedMedsToolkit.pdf>
38. USA Food and Drug Administration (FDA). Safe Disposal of Medicines [Internet]. 2013 [15 July 2014]. Available from: <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/SafeDisposalofMedicines/>

Appendix 3. Example of information for customers about an unused medicines collection programme

In Finland the pharmacy unused medicines collection programme is based on legislation. According to the waste laws, the responsibility for organising the collection of medical and hazardous waste is on communities. So they have made an agreement with all community pharmacies to act as collecting points and to inform customers about how medical waste is collected. Below are the examples of the agreement between the pharmacy and the community, the document for transferring the waste and the customer information leaflet.

A3.1. Model agreement on the collection of medical waste programme by Finnish community pharmacies

(Translated by Eeva Teräsalmi)

The Association of Finnish Local and Regional Authorities, the Finnish Solid Waste Association and the Association of Finnish Pharmacies have agreed to recommend that their member organisations follow this agreement and the instructions about the collection of medical waste.

1. Contracting parties and the object of the agreement

The contracting parties are the local waste management organisation (called X) and local community pharmacy (called Y). They have agreed the practical arrangements concerning the collection of medical waste, needles, syringes and thermometers containing mercury from consumers in the community.

2. Tasks of the Pharmacy

The pharmacy acts as a cost free collecting point for medical waste (solid, liquids, ointments, aerosols, etc.), syringes, needles and thermometers containing mercury for consumers in the community.

Packages from consumers containing medical waste are put directly into specified containers. Medical waste containing iodine or thermometers containing mercury have their own containers. Customers place their own needles and syringes in the container specified for this purpose. The pharmacy has a right to refuse to take back any needles and syringes which have been abused.

The pharmacy is not obliged to take back any hazardous waste from any public or private health, dental or veterinary care institution.

Pharmacy staff should provide information to customers on how the collection programme works. The purpose of these instructions is to secure customer privacy, promote safety and prevent any drug misuse when medical waste is processed.

The following points should be included in the consumer information:

- Medicines are returned to the pharmacy without any patient information and they should be returned in a transparent, well closed plastic bag.
- Tablets and capsules are taken out of their original packages; blisters are accepted. Empty plastic and glass packages should be recycled according to the general instructions.
- Liquids can be returned in their original package.
- Medicines containing iodine should be returned in their original packages and separated from other medical waste.
- Thermometers containing mercury should be returned separately.
- Syringes and needles should be returned separately.

Pharmacy staff should ask the customer returning the waste if they have followed the instructions and if there is any waste which should have been separated. If so, it is the responsibility of the customer to separate the waste. Medical waste that is packed in wrongly can cause severe occupational health and environmental hazards and it is of utmost importance that proper information about this is given.

It is forbidden to put any kind of infectious waste, needles and syringes, chemical waste or any waste other than medical waste in the containers reserved for medical waste.

3. Medical and chemical waste produced by the pharmacy

The pharmacy is allowed to discharge its own medical waste in a well closed, transparent plastic bag. The original packages should always be removed. This is especially important when narcotics are destroyed.

Chemical waste from the pharmacy can also be discharged. Company X takes care of the transport and discharging of this waste. It should be packed in a separate box and it should be clearly labelled as chemical waste. Every container should also have a label about the contents and about the amount of waste.

4. The tasks of company X

Company X will fetch the waste at its own cost according an agreed timetable.

The containers for medical and chemical waste should be marked clearly with the name of the pharmacy.

Company X will produce the transport document for hazardous waste.

5. Contact details

For Company X and for Pharmacy Y, issues concerning the agreement, issues concerning the orders

6. Safety

Company X is responsible for the proper education of the people involved in the transport and processing of medical waste

The pharmacy has to take care that its staff know the contents of this agreement and follow it. The instructions given by Company X concerning the packaging and separating the medical waste should be followed and customers should be informed accordingly. The pharmacy is not responsible if the customer gives wrong information. Pharmacy has to pay attention to the proper and safe return processes and to the correct storage of medical waste.

7. This agreement cannot be transferred to any third party without acceptance from both parties

8. This agreement is valid....

9. Disagreements

Date and place

Signatures

A3.2 Model transport document



Kierto Ympäristöpalvelut Oy
Kerkkolankatu 40
05800 HYVINKÄÄ
Puh. 010 229 5080

www.kiorto.fi
asiakaspalvelu@kiorto.fi

TRANSPORT DOCUMENT
VASTAANOTTOLOMAKE / TIEKULJETUKSEN SIIRTOASIAKIRJA

Asiakkaan nimi	
Pvm	30.6.2014
Netti	Hyvinkää - Nummijärvi
Aluekoodi	Kierto Ympäristöpalvelut

Tilauksen nimi / COM-ELTIONS TITRENT		Lähetysosoite / BILL-TO, ADDRESS	
Asiakkaan nimi	Setsemän Veikeksen Apteekki	Lähetysosoite	Nummijärven kunta/ YMTA/ Jätehuolto
Toukokuu	Mehilämperie 2	Lähetysnumero	CEHKKUUNNIT 1715 TIE, 04111, AL. IT 15, THOU
Postinimi ja postinumero	01900 Nummijärvi	Postinimi ja postinumero	REKAMPIDULTY TO DULCET PASTE
Yhteyshenkilön ja puh.nro	09 250 4085/ Virpi Sovensalmi	Yhteyshenkilön ja puh.nro	
Yhteystiedot		Yhteystiedot	
Tilaaja	Nummijärven kunta, kahden viikon noutoajaksi	Puhelin	5313-575
Yhteystiedot		Yhteystiedot	

Pakkaus / SIZE				Määrä / AMOUNT		Tilaus / ORDER		Käsiteltävä laatu / CLASSIFICATION IS TREATED		Käsiteltävä laatu / CLASSIFICATION IS TREATED	
Pakkaus	Määrä	Tilauksen / Order ID	Tilaus / Order ID	Tilaus / Order ID	Tilaus / Order ID	Tilaus / Order ID	Tilaus / Order ID	Tilaus / Order ID	Tilaus / Order ID	Tilaus / Order ID	Tilaus / Order ID
240 170 L	1	240	240	Valhto	UN 3249 JÄTE LÄÄKEAINE, KIRVEÄ, MYRKYLLINEN, N.O.S.						
10L	1	10	10	Valhto	UN 2822 KEMKAALLIATE, LAISTELTAVA						
30L	1	30	30	Valhto	RISIKUATE						
Huomautus: Myydään 10L ja 30L riskijäteä (toimitus kansiläheisellä)											

Asiakkaan nimi	05-00 L	00-000	000-000	000	0000	LAVAPAKKAA
Tuotteen nimi	Asi	Nimi	Nimi	Nimi	Nimi	

Vakuutamme, että kuljetus on suoritettu kuljetusohjeiden mukaisesti ja että pakkaus, merkinnät ja muut tiedot vastaavat täysin. Jätteenkuljetus on suoritettu sopimukseen vastassaottomääräysten mukaisesti. Puutteita korjataan Kierro Ympäristöpalvelut Oy:n toimipisteessä. SIIRTOASIAKIRJAA ON SÄILYTTETTÄVÄ 5 VUOTTA.

Postin ja lähetysnumerit	Pvm ja lähetysnumerit	Pvm ja vastaanottajan allekirjaus
30.6.2014	30.6.2014	30.6.2014
	Juha Rafsten	

TRANSPORT DOCUMENT SHOULD BE KEPT FOR 5 YEARS

A3.3 Model information leaflet for customers

Pharmacies collect the expired and unused medicines free of charge.

All medical waste will be sent to a dangerous waste disposal unit, in order to be destroyed. The pharmacy owner is responsible for the quality of the medicines in the pharmacy. Medicines that have been dispensed to a customer cannot be reused or resold and are classified as medical waste. For this reason the pharmacy does not compensate for any medicines that have been anywhere outside the pharmacy and they are taken back only for destruction. This practice is followed by all pharmacies and is based on the guidance from medical authorities.

When returning medical waste to the pharmacy, these instructions need to be followed:

- Remove all labels and other material which contains patient information from the packages.
- Use a transparent plastic bag for packing the medicines.
- Take all the tablets and capsules out from their original packages. You can leave them in blisters. Recycle the empty glass or plastic packages.
- Liquids can be returned in their original packages.
- All medicines containing iodine must be returned separately. Examples of products containing iodine are iodine tablets, Betadine and Iodinesorb products.
- Thermometers containing mercury must be returned separately in an airtight glass container.
- Syringes and needles must be separated from the medical waste. Pack them either in a hard plastic or glass container and close it well.
- The pharmacy doesn't take back any harmful or dangerous waste other than medicines. Batteries, electronic devices and chemicals other than medicines should be recycled according the instructions provided by the relevant authorities.

Approved by the Association of Finnish Pharmacies, the Association of Finnish Local and Regional Authorities and the -Finnish Solid Waste Association, 5 April 2013

Appendix 4. Green chemistry

A4.1 Introduction

The generation of waste during the manufacture of medicines is a serious environmental issue. The pharmaceutical industry has a responsibility to use environmentally benign processes and promote sustainable development; it should never allow the environment to be destroyed for the sake of health.^{76,77,78}

Medicines development consists of two parts: basic study and clinical trials. In the basic study stage, medicinal chemistry produces drug candidates based on the research in synthetic organic chemistry. However synthesis of target compounds is the highest priority and issues around the efficiency of the synthesis and waste are not taken into consideration.^{76,77,78}

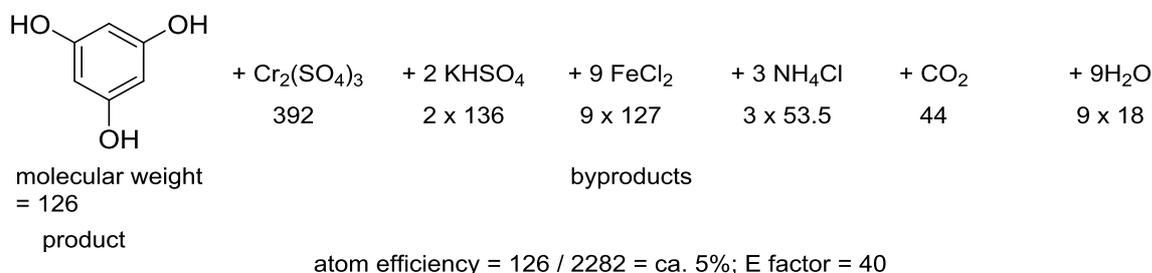
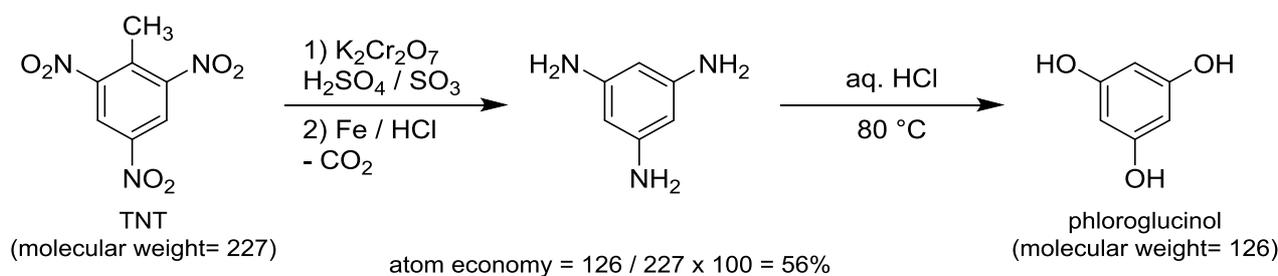
To synthesise a particular target compound, many kinds of raw materials and much energy may be consumed — and large amounts of waste may be generated proportionally. A number of drug candidates are synthesised for biological testing. Only one or fewer of 10,000–15,000 candidates is ultimately approved as a medicine. Therefore, it is necessary to improve the efficiency of research and development processes. Research performed on computer or via computer simulation has the potential to speed the rate of discovery while reducing the need for laboratory work and clinical trials. Virtual technologies such as *in silico* screening and computer modelling can deduce interactions of the candidate molecules with, for example, enzymes and ion channels, by virtual docking tests etc.^{76,77,78}

The compounds whose potential as medicines has been determined are sent for preclinical and clinical trials. In these stages, it is necessary for the compounds to be produced at larger scale (multiple kg), even though a scale of only mg or g would be sufficient for basic trials. Furthermore, after the medicine has been approved for sale, further tonnes of the medicine may be manufactured. Process chemistry plays an important role in producing the compounds safely and with appropriate quality.^{76,77,78}

A4.2 Green chemistry metrics

Although most classic methodologies cover a wide range of syntheses, they normally produce a large quantity of waste. As such, a reduction in or the complete removal of waste has become a social responsibility for the pharmaceutical industry.^{76,77,78}

Green chemistry metrics, such as atom economy, atom efficiency, E-factor, and process mass index (PMI) were introduced to estimate the efficiency of chemical processes. For example, Scheme 1 shows how phloroglucinol was synthesised by organic chemistry from the 19th century until the mid-1980s from 2,4,6-trinitrotoluene (TNT).^{76,77,78}



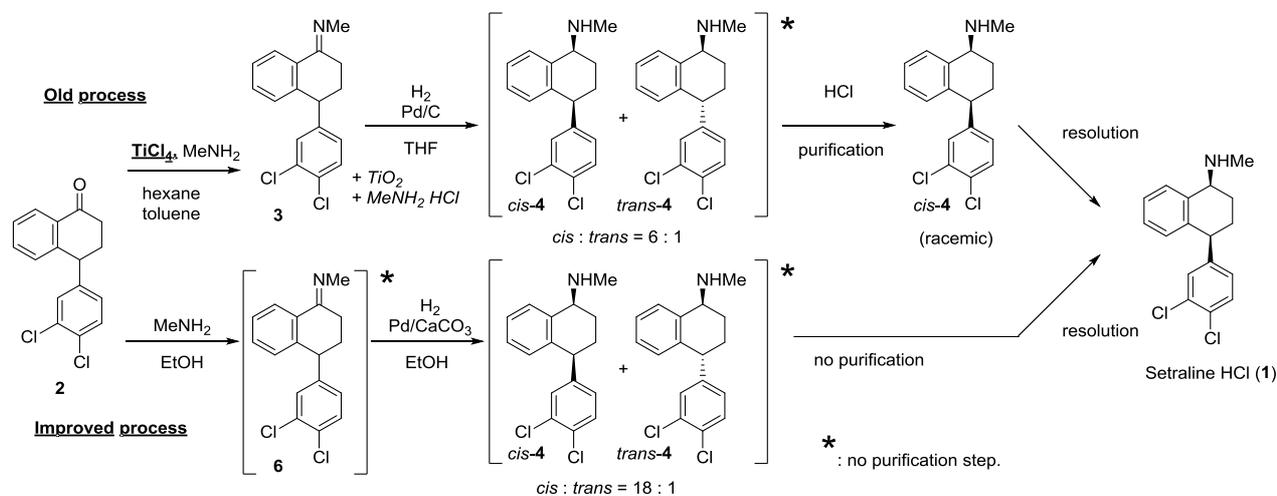
Scheme 1. Process for phloroglucinol from TNT

The quantity of waste changes according to which segment of the chemical industry it is being produced in. For example, relatively little waste is produced by the general chemical industry, but waste increases in the fine chemical and pharmaceutical industries. The E (environment)-factor was proposed as an environmental index in the kilograms of waste per kilogram of product industrial production process. The E-factor also takes fuel into consideration, as well as used reagents and solvents.^{76,77,78}

Atom economy can be estimated by simply dividing the molecular weight of a product by that of the starting material, estimated as $126/227 \times 100 = 56\%$. The E-factor takes into account all of the molecular weight of the waste generated in the process. The generation of waste becomes clear by inspecting the whole chemical equation. When calculated, 20kg of waste was produced. Atom efficiency was calculated by dividing the molecular weight of the product by the sum of that of the by-products. However, other reagents are necessary for processing and neutralisation of chemicals and wastes, such as oxidising and reducing agents. Sulphuric acid is used excessively as well, and 40kg of waste is produced in the final equations. Thus, 40kg of solid waste is produced to synthesise 1kg of phloroglucinol. In this case, the E-factor of this process is estimated as 40. The Process Mass Index (PMI) equals the total mass in a process or process step in kg divided by the mass of the product in kg ($\text{PMI} = [\text{total mass in a process or process step (kg)}] / [\text{mass of product (kg)}]$); the E-factor = $\text{PMI} - 1$. This process was abolished due to costs for waste disposal, including chromium-containing waste exceeding the selling price of the products.^{76,77,78}

Another example is a manufacturing process of sertraline hydrochloride (**1**), shown in Scheme 2. In the “old process”, the key intermediate **2** was converted to imine **2** in the presence of titanium chloride (TiCl_4). The purification was necessary to remove TiO_2 , the waste generated from TiCl_4 , and methylamine hydrochloride ($\text{MeNH}_2 \cdot \text{HCl}$). The reduction of the imine **3** in tetrahydrofuran (THF) as a solvent to give a mixture of desired *cis*-**4** and undesired *trans* isomer *trans*-**4** in a 6:1 ratio. After the removal of undesired *trans* isomer by crystallisation of the corresponding hydrochloride, the racemic sertraline (*cis*-**4**) was resolved into chiral form to produce (*S,S*)-*cis*-sertraline (**1**). In the improved process, ethanol was used as solvent in the imine formation step. The imine **6** was simultaneously crystallised from ethanol after the formation because of low solubility. As a result, this reaction proceeds simultaneously to **6** in the absence of TiCl_4 . The reduction of **6** in the same solvent ethanol gave desired *cis* isomer *cis*-**4** in better selectivity (18:1). The crude *cis*-**4** can be applied to the

resolution step directly without purification to give sertraline HCl in fewer reaction steps but improved total yield in twice. As a consequence, the total amount of solvent used in the latter process was reduced to 23,000L, one 10th of that in the old process. The emission of $\text{TiO}_2\text{MeNH}_2\text{HCl}$ (440 tonne/year) becomes zero. The use of concentrated HCl (150 tonne/year) and sodium hydroxide for the neutralisation (100 tonne/year) were reduced.



Scheme 2. Old and improved processes of sertraline HCl (1).^{61, 76, 77, 78}

A4.3 Twelve principles of green chemistry

1. **Waste prevention:** Prevent waste from the start rather than treating or cleaning it up afterwards.
2. **Atom economy:** Design synthesis methods to maximise the incorporation of intermediate materials into the final product.
3. **Safer syntheses:** Design synthesis methods to minimise the use and generation of toxic substances.
4. **Safer products:** Design chemical products to carry out their function while minimising their toxicity.
5. **Safer auxiliaries:** Minimise the use of solvents and other auxiliary substances, and make them as innocuous as possible.
6. **Energy efficiency:** Minimise the energy used in chemical processes and, if possible, carry them out at ambient temperature and pressure.
7. **Renewable feed stocks:** Use biomass and other renewable raw materials whenever practicable.
8. **Derivative reduction:** Minimise the potentially wasteful use of blocking groups and other temporary modifications of intermediates.
9. **Catalysis:** Prefer catalytic reagents — as selectively as possible — to stoichiometric reagents.
10. **Degradability:** Design chemical products for eventual disposal, so that they break down into innocuous compounds that do not persist in the environment.
11. **Pollution prevention:** Develop methods for real-time monitoring and control of chemical processes that might form hazardous substances.
12. **Accident prevention:** Choose processes and practices that minimise the potential for chemical accidents, including releases, explosions and fires.⁶²

References

76. Tucker J. Green chemistry, a pharmaceutical perspective. *Organic process research & development*. 2006;10(2):315-319.
77. Jiménez-González C, Poehlauer P, Broxterman Q, Yang B, am Ende D, Baird J et al. Key green engineering research areas for sustainable manufacturing: a perspective from pharmaceutical and fine chemicals manufacturers. *Organic Process Research & Development*. 2011;15(4):900-911.
78. Sanderson K. Chemistry: It's not easy being green. *Nature*. 2011;469(7328):18-20.

Appendix 5. Medicines and the Environment academic course at Åbo Akademi, Finland

The Medicines and the Environment academic course at Åbo Akademi, Finland is provided annually and consists of lectures with a total time varying between 16 and 22 contact hours, self-study, a two-hour film and reflection time.

The material comprises lecture material, a booklet “Medicines and the Environment” published by “Apoteket AB” in Sweden,⁷⁹ and the IT-platform where students work in discussion groups.

To pass the course, students must participate in at least 80% of the lectures, the excursion to the sewage management plant and the film session.

After passing the course students will:

- Understand how medicines enter the environment as APIs and are changing to waste in the different phases of their lifecycle
- Understand how medicines are classified according to their effects in the environment
- Understand how medicines enter the environment
- Understand how medicines can be disposed of in the different phases of their lifecycle
- Understand their own professional role in the protection of the environment

The theoretical studies consist of the following lectures:

1. Introduction to the topic
2. Pharmaceuticals in the environment: consumption of pharmaceuticals, origins and fate of pharmaceuticals in the environment, sources and pathways of pharmaceuticals to the aquatic environment, metabolism, classification possibilities, waste water treatment plants, risks for the aquatic environment, results of different studies
3. Hormones and their effects in the environment
4. Ecotoxicology
5. Sewage treatment plant — how does it work?
6. Evaluation of the environmental risks of chemicals — methods and chemical aspects
7. Antibiotics in the environment
8. Viewing of a film
9. Evaluations of the environmental risks of chemicals and medicines — classification systems
10. Green community pharmacy
11. Green medical industry
12. The role of official, evidence-based decisions — REACH

References

79. Apoteket AB, Stockholm County Council, Stockholm University. Läkemedel och miljö. Stockholm: Apoteket AB; 2005. Available at: www.apoteket.se

Appendix 6. Disaster management

Medicines are often donated or brought by health care providers and social agencies to areas affected by natural or man-made disasters. The management of medicines in such environments is difficult and the destruction of unwanted medicines is an even greater challenge. Two principles regarding pharmaceutical waste in complex humanitarian emergencies include:

1. Targeting the pharmaceutical supply to meet the needs of the community to minimise pharmaceutical waste and destruction; and
2. Managing pharmaceutical destruction in a way that minimises the potential impact on the environment and on the local population.

A6.1 Targeting donations

Inappropriate donations can be minimised by adhering to the WHO Guidelines for Medicine Donations. Donations⁸⁰ should not be based on assumed need but should be directed towards the identified requirements of the affected population. In addition, expiration dates should be greater than one year when received, unless

there is clear evidence that the recipients have the capacity to administer shorter dated pharmaceuticals within the dating.

A6.2 Destruction of pharmaceuticals

Any disposal of pharmaceuticals should comply with local government regulations when available. It is preferred to use a local hospital's medical waste disposal system if it meets required standards and reference guidelines. If no such local standards exist in the community, then the following guidelines apply:

- Avoid contaminating drinking water.
- Avoid disposing of any medicines into the sewage system. The most dangerous are disinfectants, non-biodegradable antibiotics and anti-neoplastics.
- Ensure destruction of the pharmaceutical waste in a way that reduces risk of pilfering for use or for sale.
- Ensure that pharmaceuticals are incinerated at a sufficiently high temperature to avoid release of toxic pollutants into the atmosphere.

Details of disposal methods, as well as considerations and risks associated with each type of disposal method, are described in the WHO document "Guidelines for the Safe Disposal of Unwanted Pharmaceuticals in and after Emergencies" (1999).⁸¹

References

80. Guidelines for Medicines Donations, Revised 2010: WHO
81. Guidelines for the Safe Disposal of Unwanted Pharmaceuticals in and after Emergencies, 1999 WHO

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