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Hazard/Risk Assessment

A RISK-BASED APPROACH TO MANAGING ACTIVE PHARMACEUTICAL INGREDIENTS IN MANUFACTURING EFFLUENT

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Abstract: The present study describes guidance intended to assist pharmaceutical manufacturers in assessing, mitigating, and managing the potential environmental impacts of active pharmaceutical ingredients (APIs) in wastewater from manufacturing operations, including those from external suppliers. The tools are not a substitute for compliance with local regulatory requirements but rather are intended to help manufacturers achieve the general standard of "no discharge of APIs in toxic amounts." The approaches detailed in the present study identify practices for assessing potential environmental risks from APIs in manufacturing effluent and outline measures that can be used to reduce the risk, including selective application of available treatment technologies. These measures either are commonly employed within the industry or have been implemented to a more limited extent based on local circumstances. Much of the material is based on company experience and case studies discussed at an industry workshop held on this topic. *Environ Toxicol Chem* 2015;9999:1–10.

Keywords: Active pharmaceutical ingredient Wastewater effluent Maturity path

INTRODUCTION

The presence of active pharmaceutical ingredients (APIs) in the environment has received wide attention over the past 2 decades as increasingly sensitive analytical methods have shown the widespread presence of these compounds throughout aquatic ecosystems at low, nanograms per liter concentrations [1]. There are 3 main pathways by which APIs can reach the environment. The primary pathway is through normal patient use and excretion of medicines or their metabolites into sewer and wastewater treatment systems [2]. The vast majority of pharmaceutical compounds found in water systems are a result of this pathway, and potential exposure via this pathway has been the focus of the majority of risk assessments on APIs in the environment to date. A second, lesser pathway is through improper disposal of unused or expired medicines by consumers flushing them to wastewater [3]. In contrast, the environmentally preferred methods for disposal of unused or expired medicines are through household trash or medicine "take-back" programs, and it should be noted that these disposal methods do not contribute appreciably to the total amount of medicines discharged to the environment [2–4]. The third pathway through which medicines can reach the environment is from the facilities where the products are manufactured, formulated, or packaged, either directly by the facility after on-site treatment or indirectly through a municipal wastewater treatment system, or a combination of both. This third pathway is the main focus of the present study.

Pharmaceuticals in the environment

Globally and regionally, the contribution of pharmaceutical manufacturing activities to the total amount of pharmaceuticals released into the environment is low when compared with the amount excreted by patients [3]. At the local level, however, it is recognized that manufacturing discharges can cause localized "hot spots" unless these are adequately assessed and controlled by manufacturers. Reports of APIs in water from pharmaceutical manufacturing in the European Union [5,6], the United States [7], India, and elsewhere [8,9] indicate that concentrations have reached milligrams per liter levels when wastewater discharges are not sufficiently controlled at

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facilities, highlighting the importance of effective control of API emissions from manufacturing, both in production of the API itself and in its formulation into drug products for patient use. Manufacturers should ensure that environmental control is an essential criterion used in awarding work to either subsidiaries or third-party organizations, no matter where in the world they may be located.

It is likely that APIs are present in the wastewater of virtually all locations where the occupants are using medicines, and options to prevent pharmaceuticals from entering domestic sewage are not well understood. Similarly, public wastewater treatment plants (WWTPs) may reduce, but not completely eliminate, API residues from domestic wastewater. Practically all chemical compounds used in households are expected to be present either unchanged or as degradation products at trace levels in the effluent discharged from WWTPs [10]; additional information on wastewater and sludge treatment associated with removal of pharmaceuticals is available at the Water Environment Research Foundation website [11].

An increasing number of reports of the occurrence of pharmaceuticals in the environment, accompanied by commentary on the potential significance of this in terms of both environmental impact and human health, have resulted in major research projects and regulatory initiatives. A widely reported European review of the issue, the Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters (KNAPPE) report of 2008 [12], was produced under the European Commission Research Framework Programme 6 funding process. This was followed by 2 Framework Programme 7 projects, PHARMAS [13] and CYTOTHREAT [14], which were completed in 2013. Most recently, the pharmaceutical industry and the European Commission awarded a 4-yr jointly funded EcoRiskPrediction project, Intelligence-led Assessment of Pharmaceuticals in the Environment, under the Innovative Medicines Initiative, which began in 2015 [15].

In the United States, a single pharmaceutical (nitroglycerin) appeared for the first time on the draft US Environmental Protection Agency's (USEPA's) Contaminant Candidate List 3 in 2008 [16]. However, while the final Contaminant Candidate List 3 included 10 pharmaceuticals—1 antibiotic (erythromycin) and 9 hormones (17-α-estradiol, 17-β-estradiol, equilenin, equilin, estriol, estrone, ethinyl estradiol, mestranol, and norethindrone) [17]—the third unregulated contaminant monitoring regulation retained only 5 of the final Contaminant Candidate List 3 hormones (17β-estradiol, equilin, estriol, estrone, and ethinyl estradiol) and added 2 others (testosterone and 4-androstene-3,17-dione) [18]. The USEPA-proposed Contaminant Candidate List 4 [19], issued in early 2015, includes the 10 APIs from the final Contaminant Candidate List 3 that are associated with human and animal health products. Because complete reporting and analysis of the unregulated contaminant monitoring regulation 3 data are not due until 2016, it is unclear whether any pharmaceuticals will be proposed for rulemaking due to their low detection frequencies and low measured concentrations. Three pharmaceuticals (estradiol, ethinyl estradiol, and diclofenac) were nominated as priority substances under the European Union's Water Framework Directive in 2012 and placed on a watch list for analytical monitoring starting in 2013 [20]. In 2011, the World Health Organization published a report that concluded that "discernible risks to health arising from trace levels of pharmaceuticals in drinking-water are extremely unlikely" [21].

Notwithstanding the above considerations, the pharmaceutical industry acknowledges that all stakeholders have a legitimate interest in understanding the potential for human health and environmental effects resulting from trace amounts of APIs in the environment, and we support further scientific study to better understand the implications of trace amounts of these compounds on the environment. Pharmaceuticals are just one subset of multiple emerging environmental pollutants. However, given the demonstrated presence of pharmaceuticals in the environment, coupled with the high public awareness of medicines, it is perhaps not surprising that they have attracted a great amount of attention. Although a substantial body of peer-reviewed research studies suggests that impacts to people are unlikely [3,21] and that impacts to aquatic organisms occur only under limited circumstances, we acknowledge the concern that these trace levels might present a risk to the health of aquatic organisms.

EcoPharmacoStewardship

Across our industry, we make a vast and diverse portfolio of products, each of which can have environmental impacts. Good stewardship includes understanding the potential environmental and social implications and employing life-cycle thinking and tools to minimize any potential environmental risks—from the early stages of product design to formulation and manufacturing to the product's impacts during use and final disposal of residual product.

The pharmaceutical industry has developed an EcoPharmacoStewardship framework that applies the widely accepted principles of product stewardship. The 3 pillars of the framework are extended environmental risk assessment, extension of the scientific knowledge base (Intelligence-led Assessment of Pharmaceuticals in the Environment), and control of effluent emissions from manufacturing, which is the focus of the present article.

Specific activities to control effluent emissions include evaluation of risk based on substance properties and environmental exposure, development of technical guidance on appropriate treatment technologies, and benchmarking internal and external manufacturers to identify best practices to reduce emissions. Different practices exist among pharmaceutical manufacturing companies (even within facilities of the same company) and external supplier facilities. Many of these differences are the result of the type of API being produced and its inherent hazards, the physical location of the facility and the receiving water body, the type of wastewater treatment facilities available, and other factors that may affect the final concentration of API that reaches the surface water.

One approach to managing these many variables and to ensuring that appropriate attention is given to this activity is through the use of a "maturity ladder." Conceptually, the maturity ladder is a stepwise approach of increasing capability, whereby sites progress from implementing the minimum requirements to legally operate the facility and advance to assessing and managing risk to the supply chain from potential API discharges from the facility. Further progress to mature facilities should be made by ongoing effort to identify and evaluate potential improvements in manufacturing and reductions in emissions, which can be aided by benchmarking practices with peers. A representative 6-step maturity ladder for companies and external suppliers to ensure that wastewater is appropriately managed is shown in Figure 1. It should be emphasized that the detail of this figure will vary from site to site, since clearly not all sites have the same facilities and may operate differently.

As a site progresses up the maturity ladder and implements these activities, the amount of the pharmaceuticals in manufacturing emissions and their potential environmental impact will be reduced (Figure 1).

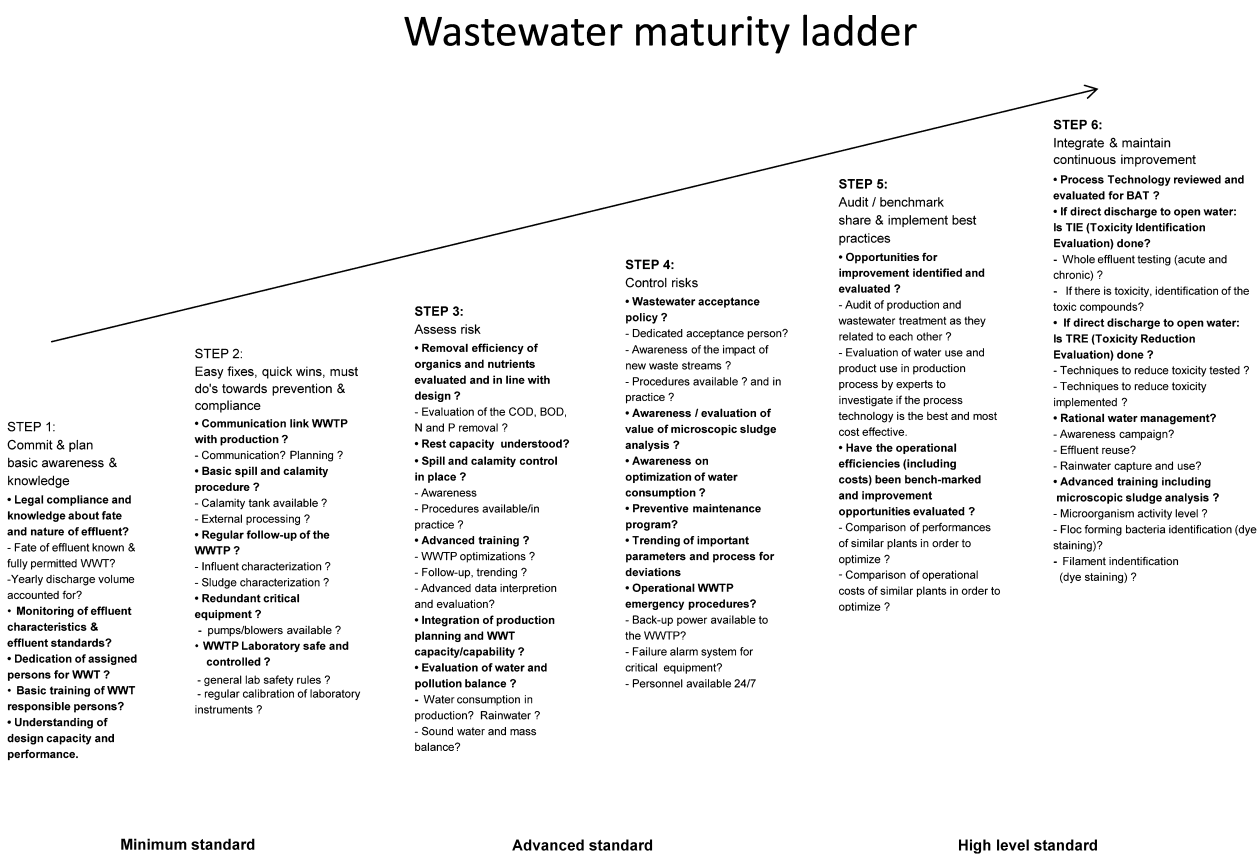

Figure 1. Wastewater maturity ladder. BAT = best available techniques; BOD = biochemical oxygen demand; COD = chemical oxygen demand; WWT = wastewater treatment; WWTP = wastewater treatment plant.

Further study on manufacturing effluents is warranted

Most API manufacturing locations worldwide have secondary (biologic) treatment for their wastewater either on site or off site in a municipal WWTP. Under the right growth conditions (e.g., pH, temperature, nutrient, absence of inhibitory or toxic compounds), diverse microorganism populations can biodegrade or cometabolize APIs. Under aerobic conditions, the microorganisms liberate the carbon, nitrogen, oxygen, and other components of the API to produce cell matter and carbon dioxide, water, nitrates/nitrites, and so forth, thereby either breaking down the API or altering the pharmacologic activity of the API. Under anaerobic conditions, the microorganisms use the carbon and other components of the API to produce cell matter and methane, water, and so forth. Not all APIs will be (completely) degraded by biological treatment, and some will not degrade at all [1,22]. Active pharmaceutical ingredients can also adhere or adsorb to the microbial flocks (biosolids) and be removed from the wastewater by sedimentation.

Manufacturing regulations pertaining to wastewater, such as the European Union's Industrial Emissions Directive [23] and the US National Pollutant Discharge Elimination System regulations [24], generally apply to pharmaceutical production. However, many socially and environmentally responsible companies go beyond compliance with the basic regulatory requirements for chemical manufacturers (e.g., control of pH, biological oxygen demand, chemical oxygen demand) and establish environmental protection goals to evaluate potential environmental risk from production of their product. To that end, these leaders in the industry are committed to minimizing the risk from APIs discharged in the wastewater from pharmaceutical manufacturing sites. They assess pharmaceutical manufacturing wastewaters for the concentration of API and/or potential toxicity to aquatic species and, where no specific regulatory limits exist, establish company exposure limits for API concentrations and/or wastewater toxicity. A significant part of the development of processes for the production of new medicines now includes optimization of the manufacturing process to minimize the environmental impact.

RISK ASSESSMENT OF API EMISSIONS

Conducting an environmental risk assessment for an API present in manufacturing effluent involves determining the predicted no-effect concentration (PNEC) and the predicted environmental concentration (PEC) and comparing these values. Generally, a PEC/PNEC ratio ≥ 1 indicates concern that the ambient exposures may be creating a risk for environmental species, and further action is necessary, beginning with refinement of the risk assessment. If river water receiving an effluent discharge is used to supply drinking water, then the potential for human exposure should be considered. In other situations (e.g., discharge into the marine environment), protecting the local environment is more likely to be the primary concern. Regulatory guidance for assessing these situations exists and should be followed [25,26]. Key to deciding if action is needed is the establishment of company water quality emissions limits, or PNECs, for the APIs that a company manufactures.

Effects assessment—Calculation of PNECs

Ecotoxicological data and professional judgment are required to identify risks to species potentially exposed to

APIs released from manufacturing facilities and to derive protective PNECs for aquatic organisms in surface waters. Other considerations include potential for effects in humans that have surface water as their source of drinking water and terrestrial organisms that could come in contact with API residues in water and solids from wastewater treatment facilities. This document is not intended to elaborate on the development of PNEC data; however, a brief overview is provided. Detailed examples of how to derive water quality limits for APIs and chemicals discharged to surface waters for Europe are provided in the European Community regulatory guidance documents and various other publications [26–30]. The US regulatory guidance for deriving water quality limits [25,31] can differ from that used in Europe [26].

Briefly, PNEC values for aquatic organisms are derived from toxicity studies in reference species that are considered representative of a wide range of environmental organisms. Assessment factors are typically applied to account for uncertainties associated with the test species and measured end points. Environmentally relevant, well-designed studies conducted using standard methods (e.g., Organisation for Economic Co-operation and Development [32], USEPA [33], or US Food and Drug Administration [34] guidelines) to assess interpretable end points relevant to population effects and employing good laboratory practices [35] are the gold standard for data quality and integrity. Research studies from the published literature may also be used; however, care must be taken to ensure that the methods and results are reliable and relevant to the ecosystem in question. The data should give a good indication of the potential impact of the API on population-level effects of survival, growth, and reproduction in aquatic species. Studies considering genomic, cellular, and/or organ effects are supportive of other data on population-relevant end points but are not normally used as the basis for PNEC derivation [26]. Once the available data have been gathered, the generally accepted approach is to use the most conservative result (i.e., lowest lethal/effect concentration for 50% mortality from acute studies or the lowest no-observed-effect concentration from chronic/reproductive studies), combined with an appropriate assessment factor, to determine the PNEC [27,28]. The European Public Assessment Report [36] for new centralized pharmaceutical market authorizations contains a summary of the data used in the environmental risk assessment. This information is publicly available on the European Medicines Agency website.

Exposure assessment: Calculation of PECs

An estimate of the PECs of APIs discharged in a site's wastewater is required to determine if an API will be below the established PNEC in the environment. The first step in calculating a PEC is to develop a comprehensive mass balance for the API along the production process(es). These mass balances are an inventory of waste streams (solid, liquid, or gaseous) that may contain the API and estimates of the concentrations of API in each waste stream. Information about waste streams can be found in process descriptions, batch records, and other documentation. Initially, concentration estimates can be calculated from the masses of API and volumes involved (e.g., mass in lot/batch, number of batches/year) using known chemical, physical, and biological properties of the compound and information on API losses, for example, from cleaning operations. Predicted environmental concentration estimations can further be confirmed analytically, in which case they are measured environmental concentrations.

Pharmaceuticals are comparatively large and chemically complex molecules. Because of their heteroatom content and multifunctional composition, they can be polar, ionizable molecules; and these properties depend on and are influenced by solution pH and ionic strength. Key characteristics regulating the distribution of APIs in waste streams and their fate and transport in aqueous environments are their physical and chemical properties and the properties that describe their depletion in WWTPs and the environment. Physical and chemical properties describe the forms of the compounds and their partitioning into various environmental compartments. The major physical and chemical properties affecting environmental fate and transport are water solubility, dissociation constant, the pH-dependent octanol–water distribution coefficient, biosolids–water distribution coefficient, Henry's law constant, and the sediment–water or soil–water distribution coefficient. The key processes that characterize the rate of transformation of organic contaminants in WWTPs and the environment are hydrolysis rate; biotransformation rate in water, biosolids, soil, and sediment; oxidation rate (via a specific oxidant); reduction rate (via a specific reductant); and photolysis rate. Most of these data are available or can be estimated from the product registration package, the safety data sheet, or information available from the manufacturer. The drug registration process requires a detailed characterization of the API during product development, including its physicochemical properties and drug stability profiles.

For a typical API manufacturing facility, calculation of PECs from various discharge scenarios is required to identify strategies for mitigation and management of API-containing wastewater prior to discharge. When measuring API concentrations in effluent, the analytical method should have an appropriate level of sensitivity to be able to detect the anticipated concentrations.

A word on whole effluent toxicity testing

"Whole effluent toxicity" is a term used to describe the adverse effects or toxicity to a population of aquatic organisms caused by exposure to an effluent, which is typically a mixture of many different substances. Survival, growth, or reproduction toxicity can be experimentally determined in the laboratory by exposing sensitive organisms (usually surrogate organisms representative of those found in the environment) to the whole effluent sample using standardized bioassays (see USEPA [37], European Commission [38,39], and OSPAR Commission [40]). Whole effluent toxicity testing is used to assess the combined effects of all constituents of a complex effluent rather than assessing the toxicity of single chemicals or constituents and can be a good predictor of acute and chronic toxicity potential of effluents. The advantage of whole effluent toxicity testing is its holistic assessment of the toxicity of the effluent as it exists in reality, in all its complexity in combination with other compounds. The disadvantage is the fact that effluent constituents will vary depending on manufacturing schedules, and the cause of any identified toxicity is often not easily determined exactly because of the complex matrix. In cases where there is day-to-day difference in the "batch process" of API production, whole effluent toxicity testing may be impractical to implement.

Assessment using the PEC/PNEC ratio for specific APIs and whole effluent toxicity testing are 2 distinct approaches, each of which has its value. Use of one does not exclude the other.

RISK MITIGATION AND MANAGEMENT

What to do if PEC/PNEC > 1

After the PEC/PNEC ratio is determined, the risk assessment can be refined if necessary. Figure 2 shows a typical decision tree that provides guidance on the actions to be taken in case the risk ratio (PEC/PNEC) is > 1.

Once a potential risk has been identified, mitigation measures outlined in Figure 2 can be evaluated. Determination of downstream dilution or removal factors can refine the impact assessment of API discharges by reducing the PEC. For effluent discharges to water bodies, appropriate dilution factors for acute and long-term exposure limits may be defined by the local environmental regulations. Typically, a representative river flow rate (m^3/d) is assumed for the PEC assessment. Seasonal variations in river flow rates may significantly change the overall risk, so the lowest seasonal river flow rate is often used as the worst case.

The following points may be considered when estimating or measuring potential API losses in the process aqueous waste and calculating the PEC:

- Estimate or measure the mass of API lost during a typical batch.
- Determine the total mass of API lost during all manufacturing campaigns in 1 yr.
- Determine number of days of manufacturing activities in 1 yr, and calculate an average PEC during the manufacturing period that can be compared with the PNEC.
- Factor in API removal from installed treatment technology, where there is evidence on the performance of such systems that are available on site.
- Measure the amount of API released during a typical manufacturing campaign. If possible, collect samples after any on-site effluent treatment.
- Ensure the limit of quantification for the chosen analytical method is sensitive enough to measure effluent concentrations that may be lower than the PNEC.
- Use the highest detected concentration from the sampling period for the risk assessment.

There are a number of important decisions that need to be made before an appropriate risk mitigation strategy can be developed. If the API is a high hazard compound, such as certain carcinogens, mutagens, cytotoxics, and some endocrine actives, a high level of containment is often required. In some cases, wastes may need to be segregated from other plant wastes and disposed of separately if the compound cannot be treated.

Another case is where the API is included in organic wastes following solvent recovery. Such residual organic wastes are usually incinerated.

A third example is where the API is processed solely in aqueous media, which will typically undergo some form of treatment (either on-site or municipal) before discharge to surface water. Consideration of the fate of the compound during such treatment is important. During wastewater treatment, a drug may be degraded via hydrolysis, oxidation, or biodegradation or may adsorb to solids during treatment and be isolated in the WWTP. Therefore, the final measured environmental concentration or PEC may be determined in the receiving stream after mixing with the effluent, in the solids generated by wastewater treatment, or in the terrestrial environment if the solids from wastewater are land-applied and could impact terrestrial organisms.

Another important exposure consideration is the nature of batch manufacturing, where the time frame of any resulting emissions will influence the PEC. Batch production may be short term, resulting in transient peak concentrations in the environment, or may be a longer campaign where continuous discharge can occur over a longer time period. Depending on the situation, either or both of these scenarios may need to be evaluated and the PEC derivation adapted accordingly.

At source control: Segregation and selective pretreatment of wastewater streams

Understanding potential emissions of APIs at their point of generation allows for better decisions to be made about segregating and controlling waste streams, which could have an adverse environmental effect if released. Analyses need to be conducted to determine whether any residuals could pose a risk either to a subsequent WWTP (i.e., inhibition or interference) or

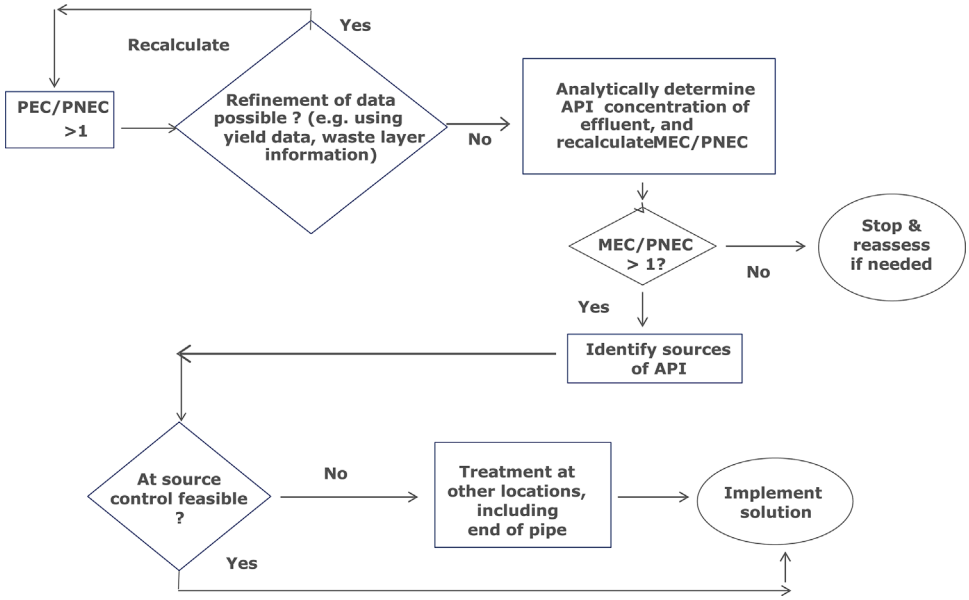

Figure 2. A decision tree providing guidance on the actions to be taken in case the risk assessment PNEC/PEC > 1. API = active pharmaceutical ingredient; MEC = measured environmental concentration; PEC = predicted environmental concentration; PNEC = predicted no-effect concentration.

to a receiving environment (i.e., lake, river, or ocean) after discharge. The following should be considered in the analysis:

- Knowledge of the waste streams: To avoid high loads of APIs entering a site's wastewater influent, a good understanding of the content of APIs in waste streams is important. Waste stream analysis can allow manufacturers to potentially optimize and implement the most effective pollution prevention and control measures.
- Equipment cleaning: Cleaning procedures can be optimized to reduce the API loading and to lower disposal costs by performing a thorough initial dry cleaning and by reducing the volume of high-strength rinses being generated. An additional separate cleaning step (prerinsing) can remove large portions of APIs from large-volume wash waters. The high-load prerinse streams can be separated and addressed subsequently by a selective technology or incineration/thermal oxidation.
- Spill control: Make sure that spills are contained and cleaned up appropriately.
- Low process yields: Modernization of the process could be an option to prevent or minimize upstream the API load of a wastewater stream. However, this may not be an alternative because of good manufacturing practice requirements.

Within the manufacture of a single API product the destination of wastewater streams may change frequently, and even more so taking into account different API production campaigns. Automated management of wastewater streams can be helpful in this regard. Waste stream analysis can allow manufacturers to optimize and implement the most effective pollution prevention and control measures. As a model practice, waste stream analysis can initially be based on flowcharts, illustrating the operations, inputs, and waste streams, along with the relevant data for each waste stream.

The importance of understanding sources of API coming from the process cannot be stressed enough. It is far better to look for process efficiency improvements that reduce the amount of APIs reaching wastewater than to look for ways to remove them once they are there.

Selection of API treatment technologies to manage wastewater streams

Many facilities in API production and final dosage production in the pharmaceutical industry rely on the use of neutralization, equalization, and biological (primarily activated sludge) treatment technologies for their wastewater treatment. Although conventional wastewater treatment technology can effectively reduce the concentrations of many APIs, more advanced technologies have been applied at manufacturing sites to remove specific compounds for which conventional treatment approaches do not work [41,42]. For refractory organic compounds (that "pass through" a biological WWTP), which potentially can cause toxicity to the WWTP or the receiving water, an evaluation of pretreatment control prior to biological treatment should be considered. End-of-pipe treatment can also be considered as an alternative, although this option is not preferred because of higher volumes, mixing with other chemicals, and lower concentrations of the compound to be treated. Active pharmaceutical ingredient removal is compound-specific and should be addressed on a case-by-case basis. Removal efficiencies of different treatments vary with different APIs, depending on the suitability of the treatment for the API and on the specific wastewater composition in each case (e.g., salinity, turbidity, organic load).

Advanced treatment technologies for the treatment of APIs include advanced oxidation processes, mass transfer processes, membrane processes, thermal processes, and advanced biological processes. It is important to include the environmental costs, such as energy requirements, waste production, and emissions to air, when considering deployment of advanced treatment technologies [43]. This is why we firmly believe that a risk-based approach to managing manufacturing effluent is important in order to avoid placing burdens on the environment that are worse than those we are trying to mitigate.

Advanced oxidation processes

In short, advanced oxidation processes oxidize the chemicals in the waste through chemical oxidation. Chlorine or Fenton's reagent reacts with electron-rich bonds of organic chemicals. Many APIs with reactive functional groups can be oxidized by free chlorine; however, in view of the formation of chlorinated by-products, it is not the most effective treatment for pharmaceutical manufacturing facilities.

Ozone is one of the most powerful chemical oxidants available. An ozone generator is located near the source to produce high ozone doses, and the dose can be rapidly changed to accommodate changing API concentrations. If treating a wastewater containing other organics, it is necessary to have biologic or other pretreatment to reduce the levels of non-API organics that scavenge the ozone. Also, residual ozone concentrations must be abated—for example, through sand bed filtration units—before discharge. Process safety and materials of construction are important considerations in the use of ozone. A combination of ozone with hydrogen peroxide will increase the quantity of hydroxyl ($^{\bullet}$OH) radicals in solution. A catalyst may be used to enhance the reaction.

Ultraviolet (UV) light oxidizes pharmaceuticals by direct photolysis and reacts with water to create $^{\bullet}$OH. The effectiveness of UV oxidation is highly dependent on the contaminant and water matrix and can be enhanced by adding hydrogen peroxide, Fenton's reagent, or ozone, which increase the quantity of OH radicals in solution.

A photocatalytic/fixed catalyst system with UV activation uses a catalyst (palladium, titanium dioxide) and hydrogen gas to oxidize APIs.

Supercritical oxidation has been employed at a few manufacturing facilities producing APIs amenable to this advanced treatment.

If the formation of toxic degradation products is suspected, then this must always be considered when deciding if an oxidation process should be employed.

Mass transfer processes (trapping the API)

These processes remove APIs from solution into the solid phase and thereby concentrate the volume of waste for treatment.

Carbon adsorption involves use of granular activated carbon or powdered activated carbon to remove organic compounds via hydrophobic interaction with the activated carbon surface. Carbon is effective for removal of some APIs (depending on log octanol–water partition coefficient) but can be depleted by other competing organics. Further, the carbon requires replacement or regeneration once the active sites are saturated with organics.

Chemical precipitation, or flocculation followed by precipitation, involves coprecipitation and surface adsorption as the primary removal mechanisms. These methods usually result in low removal rates (i.e., $<20\%$) for most API components.

Ion exchange resins use exchange materials, which can be customized for API compound selectivity. This method can be cost-effective when specific API compounds can be targeted. However, resin regeneration must be evaluated to ensure that the option is economically viable.

Clay adsorption uses bentonite clay modified with quaternary amines. The clay surface is coated with amines and becomes hydrophobic and organophilic, thus concentrating APIs.

Cyclodextrin is converted to an insoluble polymer, which is chemically fixed on silica (sand) or other support. There are several mechanisms whereby cyclodextrin removes APIs from water: they are best known for their host–guest interactions to trap molecules by offering a cavity in which the API molecule can enter and get trapped; there is also chemisorption caused by functional groups, and there may be some physical sorption as well on the cyclodextrin polymer.

Membrane separation

Membrane processes can be effective for large molecule separation. They generate a concentrated liquid waste for disposal or further treatment and can be effective when installed near the source to reduce the amounts of APIs going to treatment processes downstream. Membranes used for ultrafiltration and microfiltration have 0.01 μm to 1.2 μm pore sizes, those for nano-filtration have 0.004 μm to 0.01 μm pore sizes, and reverse osmosis membranes are <0.004 μm pore size.

Thermal processes

These processes concentrate API waste by evaporating the water (by heat or vacuum), generating either concentrated liquids (for incineration) or solids. Crystallization reduces the API concentration in effluent, resulting in solid material for disposal by incineration or landfill.

Liquid thermal oxidizers, which operate at 988 °C (1810 °F) or higher, are designed to remove organic materials from both primary wastes (mainly spent solvents) and secondary wastes (mainly water). These refractory-lined vessels feature a vortex burner section, where primary wastes are introduced, followed by a main oxidation chamber, where secondary wastes are introduced. Thermal oxidizer gas-cleaning systems include a quench tank, separator, and scrubbers to control oxidizer exhaust gas system.

Incineration is the thermal destruction of API waste fluids or concentrated API slurries. Although this kind of disposal assures complete destruction of APIs, it is a high-cost waste disposal technology and can potentially generate greenhouse gas emissions.

Sonolysis (ultrasound) produces thermal reactions in the liquid waste (inside the collapsing cavitation bubble). This technique is highly effective for low-volume/high-concentration applications for certain APIs.

Advanced biological processes

Membrane bioreactors use a microfiltration membrane to separate the solids from the liquid instead of using gravity settling to separate the biomass from the supernatant. Membrane bioreactors operate at high biomass concentrations and longer sludge ages than processes that use gravity settling. There are advantages with membrane bioreactors for degrading organic compounds that require a long contact time and acclimation period. Membrane bioreactor technology is also experimentally investigated for anaerobic treatment of pharmaceutical production wastewaters.

Advanced fluidized composting is an emerging technology that uses a thermophilic high-rate biologic process at 35 °C to 50 °C. Advanced fluidized composting operates at high biomass concentrations and an extremely long sludge age. The biosolids mineralize, and there is very little biosolid wasting and disposal.

Wastewater treatment in the pharmaceutical industry

The Pharmaceutical Research and Manufacturers of America initiated research in 1999 to evaluate the fate and pathways of APIs in surface water. A major component of this effort was the development of a comprehensive database that included treatment performance references. Other organizations have also developed treatment databases for pharmaceuticals [12,23,41,42]. There are relatively few publications on in-plant controls/treatment at pharmaceutical manufacturing facilities in the peer-reviewed literature, but the reviews by Deegan et al. [43] and Martz [44] and the report jointly published by KWR Nieuwegein and STOWA [45] discuss considerations for treatment of API-containing wastewater.

Survey information collected by the USEPA [46] and the European Commission [38,47] indicates large portions of the bulk API production and final dosage production in the pharmaceutical industry rely on the use of neutralization, equalization, and biological (primarily activated sludge) treatment technologies as the basis of control within the pharmaceutical sector. In some cases, in-plant treatments, such as granular activated carbon, acid/alkaline hydrolysis, and ozonation, have been utilized to treat specific APIs to meet either local regulations or specific water quality objectives/targets identified by environmental risk assessments.

Whether or not a particular wastewater stream can be discharged directly to a biological WWTP is an important production issue for any site. To properly reach this decision, a discharger must evaluate whether a wastewater has the potential to cause a toxic effect in an activated sludge system at the concentrations expected to be present (with a presumed safety factor) and then assess the biodegradation/removability of the API.

In general, refractory organic loads of a wastewater stream that simply "pass through" a biological WWTP more or less unchanged should trigger an evaluation of pretreatment control prior to biological treatment. To assess the removability of the individual API, consideration should be given to an appropriate test method [48], or equivalent, to characterize the total effect of all elimination mechanisms in a biological treatment plant. Therefore, 2 main strategies are usually available for pretreatment: elimination of refractory loadings (generally collection at the source followed by treatment) or enhancing the biodegradability of loadings.

Although municipal WWTPs may not be specifically designed to remove APIs, the treatment process units used at these plants (secondary biological treatment units using activated sludge) do remove certain APIs to some extent [49–54].

Consideration of external suppliers

Most companies have created complex global supply chains to manage production and distribution of their products. It is the responsibility of each individual supplier to ensure that API losses and environmental impacts from their operations are assessed in accordance with legal and regulatory requirements and are managed appropriately. To that end, it is prudent for companies to provide available data and information related to environment, health, and safety to all members of the supply

chain so that systems are in place to address potential environmental impacts in a responsible manner. One resource for managing the supply chain in general is the Pharmaceutical Supply Chain Initiative developed by a group of major pharmaceutical companies for all those involved in the pharmaceutical supply chain. For more information, see the Pharmaceutical Supply Chain Initiative website [55].

The fundamental approach to risk assessment for outsourced APIs is the same as that for internal API manufacturing facilities. The process for defining PECs and PNECs is the same in either case, although a key determinant of the reliability of the risk assessment lies in the technical expertise of the parties performing the assessment.

There are 3 main types of external supplier relationships. In the first type, the supplier is carrying out a process solely for the contracting company using a process developed by that company. In this situation, available mass balance information as well as key PEC parameters, such as batch yield, losses to solid versus liquid, and aqueous versus organic streams, should be provided to the supplier. Treatability parameters, such as WWTP removability, may also be provided if known. Additionally, appropriate PNECs should be determined and communicated to the supplier. This leaves only site-specific factors (i.e., flow/dilution volumes, treatment type, local ecosystem/species) to be determined by the supplier. In the second type of relationship, the supplier is manufacturing an API using a process developed by the supplier. In this case, much of the process-related information needed for the risk assessment will be available from the supplier, and only API compound–specific data need to be provided to the supplier by the contracting company. The third type of relationship is one where the API is treated as a commodity, freely available on the open market. In this case, the API supplier is like any other commodity supplier. Some form of capability assessment and possibly subsequent education may be warranted. This can take the form of a guidance document or presentation describing the steps and techniques necessary to complete an environmental risk assessment. The supplier should be referred to other available guidance resources.

An additional consideration for the supplier is whether to assess the environmental risk holistically for the entire operation or to isolate the production done for the contracting company alone. For example, if several APIs are produced by a supplier, the assessment could be for the specific API and quantity supplied to the requesting company only. Alternatively, an understanding of the overall risk to the environment from the whole operation might be desired. Where a facility manufactures multiple APIs, which may be discharged simultaneously, or where there are several different manufacturers potentially discharging APIs to the same receiving environment, some consideration should be given to the local facility impact assessment. As previously noted, the Pharmaceutical Supply Chain Initiative website [55] offers some guidance in this area. The maturity ladder (Figure 1) is another resource to assist a manufacturing facility to assess and manage the risk from APIs discharged in wastewater. A clear action plan with agreed-upon timelines ensures that both the supplier and the company understand how to move forward and meet expectations. Building capability at suppliers might be necessary to increase awareness on how to use data provided, how to conduct an environmental risk assessment, or techniques for reducing API losses. Of course, these methods require the consent, participation, and transparency of the supplier. It also takes time to develop relationships and mutual understanding of the protection goals, as well as to develop any new treatment steps or other mitigation measures to achieve them.

A risk-based prioritization is often useful to help target resources appropriately. Such prioritization may consider the regional application of the program. When considering application of the program by region, a company should consider the types of facilities that will be expected to implement the program, such as all manufacturing facilities; only those engaged in bulk manufacturing of APIs, formulation activities, or packaging; pilot plants; and research facilities. Expectations for implementation of programs to control the discharge of APIs at facilities that are owned by external suppliers in the supply chain also need to be defined.

TRANSPARENCY

A key document available at manufacturing facilities that communicates information related to the environmental fate and effects of APIs is the safety data sheet. The safety data sheet should provide a minimum data set of chemical, physical, biological, and toxicological data available on the API. In addition to the safety data sheet, environmental data should be accessible to those who need the data. This could include providing such information on a company website, presenting the material at scientific conferences, and publishing the data and assessments in the scientific literature. These latter initiatives contribute to the overall efforts of the scientific community to better understand the environmental impacts of APIs and to devise more effective methodologies and technologies to assess, minimize and manage them.

CONCLUSION

Successful management of manufacturing effluent supports the pharmaceutical industry's overall EcoPharmacoStewardship framework to minimize the risk from exposure to pharmaceuticals in the environment.

The first step is to understand the protection goals for a site such that humans and/or the environment are not harmed. Widely accepted risk-assessment principles can be easily adapted for this purpose; however, specific considerations of intermittent discharges from batch processing and characteristics of the local receiving environment are generally key for undertaking environmental risk assessment in a manufacturing context. Where several compounds are likely to be released simultaneously, consideration of mixture toxicity may be required; however, apart from possibly using whole effluent toxicity methods (which have their strengths and limitations), this is currently extremely difficult to do in practice and is an area for future research. Additional areas of research relevant to treatment of manufacturing effluents can be found in Boxall et al. [56] and Rudd et al. [57].

Development and implementation of a program to manage the discharge of APIs in manufacturing effluent are key to managing these risks. This requires a company to commit to providing adequate resources and expertise to position itself on the appropriate step of the maturity ladder for the specific facility and APIs being produced, including external suppliers.

Furthermore, the responsibility for overall management must be assigned to an accountable individual with the authority for its implementation and the ability to integrate program elements into ongoing activities throughout the company. The maturity ladder is a resource for pharmaceutical companies and can be used with external suppliers.

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Data availability—This is a best practices paper; as such, no new data are presented.

REFERENCES

1. Monteiro SC, Boxall ABA. 2010. Occurrence and fate of human pharmaceuticals in the environment. *Rev Environ Contam Toxicol* 202:53–154.
2. Tischler L, Buzby M, Finan DS, Cunningham VL. 2013. Landfill disposal of unused medicines reduces surface water releases. *Integr Environ Assess Manag* 9:142–154.
3. Caldwell DJ. 2016. Sources of pharmaceutical residues in the environment and their control. In Hester RE, Harrison RM, eds, *Pharmaceuticals in the Environment*, Vol 41—Issues in Environmental Science and Technology. Royal Society of Chemistry, Cambridge, UK.
4. Cook SM, VanDuinen BJ, Love NG, Skerlos SJ. 2012. Life cycle comparison of environmental emissions from three disposal options for unused pharmaceuticals. *Environ Sci Technol* 46:5535–5541.
5. Cardoso O, Porcher JM, Sanchez W. 2014. Factory-discharged pharmaceuticals could be a relevant source of aquatic environment contamination: Review of evidence and need for knowledge. *Chemosphere* 115:20–30.
6. Sanchez W, Sremski W, Piccini B, Palluel O, Maillot-Marechal E, Betoulle S, Jaffal A, Ait-Aissa S, Brion F, Thybaud E, Hinfray N, Porcher JM. 2011. Adverse effects in wild fish living downstream from pharmaceutical manufacture discharges. *Environ Int* 37:1342–1348.
7. Phillips PJ, Smith SG, Kolpin DW, Zaugg SD, Buxton HT, Furlong ET, Esposito K, Stinson B. 2010. Pharmaceutical formulation facilities as sources of opioids and other pharmaceuticals to wastewater treatment plant effluents. *Environ Sci Technol* 44:4910–4916.
8. Larsson DG. 2014. Pollution from drug manufacturing: Review and perspectives. *Philos Trans R Soc Lond B Biol Sci* 369:20130571.
9. Larsson DG, de Pedro C, Paxeus N. 2007. Effluent from drug manufactures contains extremely high levels of pharmaceuticals. *J Hazard Mater* 148:751–755.
10. Fent K, Weston AA, Caminada D. 2006. Ecotoxicology of human pharmaceuticals. *Aquat Toxicol* 76:122–159.
11. Water Environment Research Foundation. 2015. WERF compounds of emerging concern research. Alexandria, VA, USA. [cited 2015 July 08]. Available from: http://www.werf.org/c/KnowledgeAreas/TraceOrganics/Trace_Organics_Research_at_a_Glance.aspx
12. European Commission. 2008. Knowledge and need assessment on pharmaceutical products in environmental waters (KNAPPE contract no. 036864). D6.6 KNAPPE Final Report. EUR 20418 EN/4. Brussels, Belgium.
13. Ecologic Institute. 2013. Ecological and Human Health Risk Assessments of Drugs in the Environment (PHARMAS). [cited 2015 July 08]. Available from: http://www.ecologic.eu/4276
14. European Commission. 2012. Community Research and Development Information Service (CORDIS). CytoThreat Report Summary. Brussels, Belgium.
15. Innovative Medicines Initiative. 2015. Intelligent assessment of pharmaceuticals in the environment. [cited 2015 July 08]. Available from: http://www.imi.europa.eu/content/ipie
16. US Environmental Protection Agency. 2008. Drinking Water Contaminant Candidate List 3—Draft. *Fed Reg* 73:9628–9654.
17. US Environmental Protection Agency. 2009. Drinking Water Contaminant Candidate List 3—Final. *Fed Reg* 74:51850–51862.
18. US Environmental Protection Agency. 2012. Revisions to the Unregulated Contaminant Monitoring Regulation (UCMR 3) for public water systems. Final Rule. 40 CFR Parts 141 and 142. *Fed Reg* 77:26072–26101.
19. US Environmental Protection Agency. 2015. Drinking Water Contaminant Candidate List 4—Draft. *Fed Reg* 80:6076–6084.
20. European Commission. 2012. Proposal for a directive of the European Parliament and of the Council amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy. COM(2011) 876 final, 2011/0429 (COD). Brussels, Belgium.
21. World Health Organization. 2011. Pharmaceuticals in drinking water. WHO/HSE/WSH/11.05. Geneva, Switzerland.
22. Gardner M, Comber S, Scrimshaw MD, Cartmell E, Lester J, Ellor B. 2012. The significance of hazardous chemicals in wastewater treatment works effluents. *Sci Total Environ* 437:363–372.
23. European Commission. 2010. Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control). *Official J Eur Union* L334:17–119.
24. US Environmental Protection Agency. 2014. EPA Administered Permit Programs: The National Pollutant Discharge Elimination System. 40 CFR Part 122. Government Printing Office, Washington, DC.
25. US Environmental Protection Agency. 1995. Final Water Quality Guidance for the Great Lakes System. Final Rule. 40 CFR Part 9. *Fed Reg* 60:15365–15425.
26. European Commission. 2011. Common implementation strategy for the Water Framework Directive (2000/60/EC): Technical guidance for deriving environmental quality standards. Guidance document no. 27. Technical report 2011-055. Brussels, Belgium.
27. European Chemicals Agency. 2011. Guidance on information requirements and chemical safety assessment, part B: Hazard assessment, Ver 2.1. Helsinki, Finland.
28. European Medicines Evaluation Agency. 2006. Guideline on the environmental risk assessment of medicinal products for human use. EMEA CHMP/SWP/4447/00. London, UK.
29. Murray-Smith RJ, Coombe VT, Gronlund MH, Waern F, Baird JA. 2012. Managing emissions of active pharmaceutical ingredients from manufacturing facilities: An environmental quality standard approach. *Integr Environ Assess Manag* 8:320–330.
30. Schwab BW, Hayes EP, Fiori JM, Mastrocco FJ, Roden NM, Cragin D, Meyerhoff RD, D'Aco VJ, Anderson PD. 2005. Human pharmaceuticals in US surface waters: A human health risk assessment. *Regul Toxicol Pharmacol* 42:296–312.
31. US Environmental Protection Agency. 1995. Water quality guidance for the Great Lakes system: Supplementary information document (SID). EPA 820/B-95/001. Washington, DC.
32. Organisation for Economic Co-operation and Development. 2014. Effects on biotic systems. *OECD Guidelines for the Testing of Chemicals*. Paris, France.
33. US Environmental Protection Agency. 2014. Toxic Substances Control Act (continued): Environmental Fate Testing Guidelines. 40 CFR Part 797. Government Printing Office, Washington, DC.
34. US Food and Drug Administration. 2006. Guidance for industry: Preparing a claim of categorical exclusion or an environmental assessment for submission to the Center for Food Safety and Applied Nutrition—Attachment 1. Washington, DC.
35. US Food and Drug Administration. 2014. Good Laboratory Practice for Nonclinical Laboratory Studies. 21 CFR Part 58. Government Printing Office, Washington, DC.
36. European Medicines Agency. 2015. European public assessment reports. London, UK. [cited 2015 July 08]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125
37. US Environmental Protection Agency. 2014. Guidelines Establishing Test Procedures for the Analysis of Pollutants. 40 CFR Part 136. Government Printing Office, Washington, DC.
38. European Commision. 2006. Reference document on best available techniques for the manufacture of organic fine chemicals. Seville, Spain.
39. European Commision. 2014. Best available techniques (BAT) reference document for common waste water and waste gas treatment/management systems in the chemical sector (final draft July 2014). Seville, Spain.
40. OSPAR Commision. 2007. Practical guidance document on whole effluent assessment. Publication no. 316/2007. London, UK.

41. US Environmental Protection Agency. 2010. Treating contaminants of emerging concern—A literature review database. EPA 820/R-10/002. Washington, DC.
42. US Environmental Protection Agency. 2010. *Contaminants of Emerging Concern (CECs) Removals Database*, Ver 3 (Microsoft Access®). Washington, DC.
43. Deegan AM, Shaik B, Nolan K, Urell K, Oelgemöller M, Tobin J, Morrissey A. 2011. Treatment options for wastewater effluents from pharmaceutical companies. *Int J Environ Sci Tech* 8:649–666.
44. Martz M. 2012. Effective wastewater treatment in the pharmaceutical industry. *Pharm Eng* 32:1–12.
45. Derksen A, ter Laak T. 2013. Human pharmaceuticals in the water cycle. KWR 2013-062 and STOWA 2013-23. KWR Nieuwegein and STOWA, Amersfoort, The Netherlands.
46. US Environmental Protection Agency. 1998. Effluent guidelines: Pharmaceutical manufacturing—Development document for final effluent limitations guidelines and standards. EPA 821/R-98/005. Washington, DC.
47. European Commission. 2006. Integrated pollution prevention and control: Reference document on best available techniques for the manufacture of organic fine chemicals. Brussels, Belgium.
48. Organisation for Economic Co-operation and Development. 1992. Test No. 302B: Inherent biodegradability—Zahn-Wellens/EVPA test. *OECD Guidelines for the Testing of Chemicals*. Paris, France.
49. Gros M, Petrovic M, Ginebreda A, Barcelo D. 2010. Removal of pharmaceuticals during wastewater treatment and environmental risk assessment using hazard indexes. *Environ Int* 36:15–26.
50. Kostich MS, Batt AL, Lazorchak JM. 2014. Concentrations of prioritized pharmaceuticals in effluents from 50 large wastewater treatment plants in the US and implications for risk estimation. *Environ Pollut* 184C:354–359.
51. Lundstrom E, Adolfsson-Erici M, Alsberg T, Bjorlenius B, Eklund B, Laven M, Breitholtz M. 2010. Characterization of additional sewage treatment technologies: Ecotoxicological effects and levels of selected pharmaceuticals, hormones and endocrine disruptors. *Ecotoxicol Environ Saf* 73:1612–1619.
52. Malinowski JL, Chaplick JP, O'Brien PJ. 2009. Treatment technologies for the removal of active pharmaceutical ingredient microconstituents from pharmaceutical process wastewaters. *Proceedings*, Water Environment Federation, Microconstituents and Industrial Water Quality Conference, Baltimore, MD, USA, 26–29 July 2009, pp 284–303(220).
53. Oppenheimer J, Stephenson R. 2006. Time out: Longer solids retention times can remove some PPCPs. *Water Environment and Technology* 18:77–82.
54. Sarp S, Chon K, Kim IS, Cho J. 2011. Advanced treatment of membrane bioreactor (MBR) effluents for effective wastewater reclamation. *Water Sci Technol* 63:303–310.
55. Pharmaceutical Supply Chain Initiative. 2015. PSCI: Pharmaceutical Supply Chain Initiative. [cited 2015 July 08]. Available from: http://www.pharmaceuticalsupplychain.org
56. Boxall AB, Rudd MA, Brooks BW, Caldwell DJ, Choi K, Hickmann S, Innes E, Ostapyk K, Staveley JP, Verslycke T, Ankley GT, Beazley KF, Belanger SE, Berninger JP, Carriquiriborde P, Coors A, Deleo PC, Dyer SD, Ericson JF, Gagne F, Giesy JP, Gouin T, Hallstrom L, Karlsson MV, Larsson DG, Lazorchak JM, Mastrocco F, McLaughlin A, McMaster ME, Meyerhoff RD, Moore R, Parrott JL, Snape JR, Murray-Smith R, Servos MR, Sibley PK, Straub JO, Szabo ND, Topp E, Tetreault GR, Trudeau VL, Van Der Kraak G. 2012. Pharmaceuticals and personal care products in the environment: What are the big questions? *Environ Health Perspect* 120:1221–1229.
57. Rudd MA, Ankley GT, Boxall AB, Brooks BW. 2014. International scientists' priorities for research on pharmaceutical and personal care products in the environment. *Integr Environ Assess Manag* 10:576–587.