Ocean & Coastal Management 127 (2016) 74–80

Contents lists available at ScienceDirect

Ocean & Coastal Management

journal homepage: www.elsevier.com/locate/ocecoaman

A comparative evaluation of environmental risk assessment strategies for pharmaceuticals and personal care products

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ARTICLE INFO

Article history:
Received 16 August 2015
Received in revised form
5 April 2016
Accepted 14 April 2016
Available online 26 April 2016

Keywords:
Pharmaceuticals
Marine environment
Environmental risk assessment

ABSTRACT

With the increased concern of potential threats triggered by the occurrence of pharmaceuticals and personal care products (PPCPs) in the environment, environmental risk assessment (ERA) strategies for such compounds have considerably evolved over the past decade. Regulations are in effect or planned in several developed countries, however, there is no global standard for conducting ERAs. A review of guidelines developed by the United States Food and Drug Administration (US FDA), European Union European Medicines Evaluation Agency (EU EMEA), and Japan are presented in this paper. The methods of each protocol are compared and contrasted, thereby highlighting the strengths and weaknesses of each approach. To further assess the effectiveness of these ERAs, each protocol was carried out using actual concentrations of sulfamethoxazole (SMZ), a common sulfonamide used as an antibiotic in animals and humans, detected in four US bays. The protocols produce conflicting results regarding the possible influence of SMZ in the selected coastal environments.

1. Introduction

Pharmaceuticals and personal care products (PPCPs) are among a group of chemicals termed "contaminants of emerging concern" (CECs). CECs are not necessarily new pollutants as they may have been present in the environment for several years, but their presence and significance are only now being evaluated (Daughton, 2001). Such pollutants may have potentially devastating effects on the aquatic environment, more specifically, in coastal and marine ecosystems.

Due to their medical properties, PPCPs have an inherent biological effect; furthermore, they behave as persistent pollutants because of their continual infusion into the aquatic ecosystem (Harada et al., 2008; Ferrari et al., 2004; Van der Oost et al., 2003). The development of specific ecological risk assessments for pharmaceuticals began in Europe in 1993 with the Commission Regulation (65/65/EEC), which established the European Medicines Evaluation Agency (EU EMEA), issued by the European Union was amended to Directive (93/39/EEC). Under the amendment, the EMEA set a "safety value" of 10 ng/L for the predicted environmental concentration (PEC) of pharmaceuticals. This lead to the creation of the "Discussion Paper on Environmental Risk Assessment of Non-Genetically Modified Organism (Non-GMO) Containing Medicinal Products for Human Use" published by the Committee for Proprietary Medicinal Products (CPMP), part of the EU EMEA (European Agency for the Evaluation of Medicinal Products, 2001; Bound and Voulvoulis, 2004). However, the most recent "Note for Guidance on Environmental Risk Assessment of Medicinal Products for Human Uses" published in July 2003, is now under review (European Agency for the Evaluation of Medicinal Products, 2003).

Similarly, the United States Food and Drug Administration (US FDA) has regulated the license application process for new drugs by requiring the basic assessment of new pharmaceutical products. In 1995 a review of the process led to stricter regulations and the publishing of a revised environmental assessment manual in 1998 entitled, "Guidance for industry––Environmental assessment of human drugs and biologics applications" (United States Food and Drug Administration, 1998).

The United States and European Union are the only entities that have well-defined existing ERAs for PPCPs. Some countries, such as

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http://dx.doi.org/10.1016/j.ocecoaman.2016.04.013
0964-5691/

Canada or Korea, follow the procedures set forth by either the United States or the European Union. To the author's knowledge, Japan is the only other country developing an approach for the ERA of PPCPs. Several countries are just now beginning to recognize PPCPs as hazardous environmental contaminants, and therefore, have not begun the process of evaluating their ecological risk. For the present study, risk assessment procedures for PPCPs employed by the US FDA, EU EMEA, and Japan were compared, addressing the similarities and distinctions of the three approaches. In order to further highlight the variations between the three ERAs, the protocols were carried out using actual environmental concentrations of sulfamethoxazole (SMZ), a common sulfonamide used as an antibiotic in animals and humans, in selected US bays.

2. Review of environmental risk assessment procedures for PPCPs

2.1. United States Food and Drug Administration

The United States Food and Drug Administration (US FDA) is required under The National Environmental Policy Act of 1969 (NEPA) to assess the environmental impacts approving drug and biologics applications (National Environmental Policy Act, 1994). Thusly, a document titled: "Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications" was published outlining the routine of ERAs for PPCPs to be followed in the United States (United States Food and Drug Administration, 1998). For this protocol, the toxicity of a substance to organisms in the environment is evaluated following a tiered approach to environmental effects testing.

The first step of the US FDA protocol is to investigate environmental depletion mechanisms of PPCPs. For those compounds that appear to be quickly and sufficiently removed from the environment by hydrolysis or biodegradation, only a microbial inhibition test is required to assess how the compound may impact waste water treatment processes. If no rapid, complete depletion mechanism is identified for the substance, it is assumed to be a persistent compound in the environment and must be further evaluated by the tiered approach. Compounds with a high octanol/water partition coefficient (K_{OW}) are considered lipophilic and likely to bioaccumulate. For this reason, any compound with a log K_{OW} greater than or equal to 3.5 under relevant environmental conditions is immediately considered for Tier Three testing and chronic toxicity tests are initiated (United States Food and Drug Administration, 1998).

Each tier has a corresponding assessment factors (AF) which is established on valid ecotoxicity data available. For each compound, toxicity tests with an endpoint of either a median effective concentration (EC50) or median lethal concentration (LC50) are to be performed and both an expected introduction concentration (EIC) and an expected environmental concentration (EEC) must be calculated. If an appropriate test endpoint divided by the maximum expected environmental concentration (MEEC), which corresponds to whichever quantity is higher between the EIC and the EEC, is greater than or equal to the AF for that tier and there are no sublethal or observable effects, no further assessment is necessary. If, however, the ratio of the EC50 or LC50 and the MEEC is less than the AF, additional testing should be performed.

For Tier One, acute ecotoxicity testing must be performed with one suitable organism. Acute toxicity testing is also sufficient for Tier Two, however, it must be performed on a base set of organisms which, for the aquatic base set, includes a fish acute toxicity test, an aquatic invertebrate acute toxicity test and an algal species bioassay. Chronic toxicity testing is required for Tier Three. Furthermore, if sublethal effects are observed at the MEEC at any stage of the assessment, chronic toxicity testing is advised. If this occurs in Tier Three, consultation with the Center for Drug Evaluation and Research (CDER) and/or the Center for Biologics Evaluation and Research (CBER) is recommended (United States Food and Drug Administration, 1998).

2.2. European Union European Medicines Evaluation Agency

The procedure for an ERA of PPCPs in Europe follows a stepwise tiered procedure which is described in a recently published discussion paper of the CPMP of the EU EMEA (European Agency for the Evaluation of Medicinal Products, 2003). In Phase I of the EU EMEA protocol, is calculated based on a crude predicted environmental concentration (PEC) for the compound or its major metabolites. This value is derived by integrating information on predicted amounts used and specific removal rates in a sewage treatment plant (STP) or surface waters. If this PEC is below 10 ng/L, it may be assumed that the compound is present in such small levels and, therefore, presents no environmental risk, requiring no further investigation; 10 ng/L is a threshold value set by the EU EMEA. If the PEC is greater than 10 ng/L or the compound is known to pose special ecotoxic effects, Phase II testing is necessary (European Agency for the Evaluation of Medicinal Products, 2003).

Phase II is divided into two tiers. Tier A involves a review of the physicochemical and toxicological data to determine whether the compound will degrade or accumulate in the environment. Standard acute toxicity tests are performed on algae, daphnia and fish and the lowest figures available for these tests are used to calculate a predicted no-effect concentration (PNEC). The PNEC is modified by an assessment factor (AF) which is used to account for the uncertainty involved in extrapolating from the limited base set tests to more realistic conditions. The magnitude of the assessment factor is inversely proportional to the amount of data obtained. The PEC/PNEC risk quotient is then compared to one. If the ratio is less than one and no bioaccumulation risk is identified, the assessment may be concluded. However, if the ratio is greater than one, or the physicochemical properties indicate that there is a potential for the chemical to accumulate in the environment, the process continues on to the next tier. The PNEC is revised in tier B by the incorporation of chronic toxicity test concentration of at least one of the base set of fish, daphnia, or algae (European Agency for the Evaluation of Medicinal Products, 2003).

2.3. Japan

The ERA protocol employed by Japan is referred to in publications as a "first approach for risk evaluation for PPCPs". To the author's knowledge, only two studies have employed this approach, therefore, it is severely under-developed in comparison to its more superior equivalents established by the United States and the European Union. While other developed Asian countries follow the guidelines of the EU EMEA, Japan appears to be the only Asian country developing their own guidelines. According to the protocol, a PNEC is calculated using no-observed-effect concentration (NOEC) values generated from Algal Growth Inhibition (AGI) tests modified with the incorporation of an AF. Then the measured environmental concentration (MEC) is divided by the PNEC. If the risk ratio is less than 0.1, the concentration is "Acceptable"; if the ratio is between 0.1 and one, the compound "Needs further survey"; if the ratio is equal to or greater than one then the compound "Needs detailed evaluation" (Harada et al., 2008; Yamashita et al., 2006).