

Pharmaceuticals in The Environment: Recent Progresses for An Effective and Responsible Environmental Risk Management

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Summary

The presence of pharmaceuticals in the environment is a growing global concern¹. Chiesi Farmaceutici S.p.A., as a member of the European Federation of Pharmaceutical Industry Association (EFPIA), shares the widespread concern raised by the presence of pharmaceuticals in the environment and embraces the adoption of the Resolution of the European Parliament on the Strategic Approach to Pharmaceuticals in the Environment (PiE). In accordance with its commitment to operate with integrity, in a socially and environmental responsible care, Chiesi applied a tiered approach for the identification of potential environmental risks of active pharmaceutical ingredients (APIs) and related products in order to define an environmental targeted assessment strategy. In this study, all the main potential environmental exposure patterns were investigated, and specific systems to reduce and treat manufacturing discharges were identified. LC-MS analytical methods were developed to monitor and then subsequently estimate a predicted environmental concentration (PEC). As directed by EFPIA guidance², environmental fate alongside ecotoxicological studies were carried out in order to set the appropriate hazard levels and safe concentrations (PNECs: Predicted No Effect Concentrations). Preliminary monitoring campaigns were planned with the goal of refining the predicted PEC thus providing a realistic and responsible view of potential hazards and risks. The study addressed the characterization of the environmental risk in terms of the quotient PEC/PNEC which for the APIs studied was demonstrated to be below 1. Hence, the manufacturing discharges were assessed to not pose an environmental risk.

Key Message

Aligned with EFPIA guidance², Chiesi Farmaceutici provided a sustainable approach and focused on the implementation of a risk management process to identify potential environmental risks associated with active pharmaceutical ingredients. The risk quotient PEC/PNEC resulted to be below 1. An environmental risk from manufacturing discharge was reasonably excluded.

Introduction

Although pharmaceuticals enter the environment mainly as a result of patient use³, drug manufacturing and improper disposal of unused drugs contribute to increase the trace levels of pharmaceuticals in rivers, lakes, soils, and sometimes drinking water⁵. Chiesi Farmaceutici encourages actions to control, monitor and minimize the risks associated to PiE. Even in the absence of regulatory requirements, Chiesi is among various stakeholders who commit to ensuring safe pharmaceutical discharge from its manufacturing facilities. Chiesi followed three main pillars recognized as the focus for the pharmaceutical industries: identification of the potential environmental risks of proprietary APIs, analysis and set up of a monitoring system to manage the possible release of APIs in the environment, revision and refinement of the existing Environmental Risk Assessment (ERA) to comply with the new standard requirements. Analytical methods with adequate selectivity and sensitivity were developed for the preliminary analysis of the manufacturing wastewater discharges in order to determine the actual API and related product concentrations in the environment (PEC – Predicted Environmental Concentration). This study aims to assess the risk in terms of the quotient PEC/PNEC (Predicted Environmental Concentration/Predicted No Effect Concentration), by considering standard productions compared to long-term and acute ecotoxicological effects, respectively in the scope of granting a Risk Quotient (RQ) < 1. When a risk is identified (RQ ≥ 1), the selection of an area for refinement has to be planned and suitable controls and actions should be adopted. APIs presented in this study are from market authorized inhaled fixed-dose combination drug products. In details, an inhaled corticosteroid, a long-acting β_2 agonist (LABA), a short-acting β_2 adrenergic agonist and a long-acting muscarinic antagonist (LAMA) were selected.

Material and Methods

Analytical methods

LC-MS analytical methods suitable for the detection of ultra-trace levels of active ingredients and related products were developed, accounting for the complexity of the matrix to be analyzed. Depending on APIs characteristics, LC Shimadzu [e.g. Nexera series, ABSciex ExionLC, Agilent 1290 Infinity or equivalent] coupled with MS/MS and LC Thermofisher Scientific [e.g. Vanquish UHPLC or equivalent] coupled with HRMS were employed. Similarly, different stationary phases were selected depending on the APIs polarity. When deemed necessary, sample preparation was carried out by performing a 1:5 dilution of the "as is" sample in water. Water was used as diluent except for the inhaled corticosteroid sample preparation for which an organic solvent was employed in order to improve its extraction. Spiked samples were prepared in triplicate and analyzed. Since the monitoring and/or hazard thresholds found in the preliminary assessment were in the nanogram range, the limit of quantification (LOQ) was set at 10 ppt (pg/mL).

Ecotoxicological studies

In deriving the PNEC values for aquatic organisms, ecotoxicological data covering species from the three main trophic levels — algae, invertebrates, and fish — were used to ensure adequate representation of aquatic ecosystems. OECD⁴ Guidelines for the testing of chemicals were followed. A conservative approach based on chronic endpoints was applied. The selected endpoints focused on key biological effects such as survival, growth, and reproduction, providing a scientifically robust foundation for determining potential impacts on aquatic life. Toxicity endpoints (e.g. NOEC, EC₁₀, EC₅₀) were adjusted using appropriate assessment factors, in line with international guidance, to account for uncertainties such as interspecies variability, data limitations, and potential underrepresentation of sensitive species.

Results and discussion

Firstly, the predicted release concentration (PEC) was estimated based on API losses from the manufacturing facilities per year and the annual water discharge from the plant. Release from standard manufacturing campaigns was considered. A dilution factor of 100 was applied based on the geographical position of the plant, the dilution due to the discharge in the river flow and the dilution before entering in the surface water.

Having identified the aquatic compartment as the main focus for concern, ecotoxicological studies were carried out on various wildlife species such as aquatic plants (i.e. algae), invertebrates (i.e. Daphnia) and fish. Peer-reviewed literature data were evaluated. In addition, *ad hoc* ecotoxicological studies were carried out using standardized methods and applying Good Laboratory Practices (GLP). A *no-observed-effect concentration* (NOEC) was obtained, and a chronic PNEC_{surface water} was established. Following the ECHA⁵ and EFPIA² technical guidance, conservative standard safety factors were applied.

Stress tests were conducted mimicking conditions similar to the ones of the manufacturing discharge. Only for the inhaled corticosteroid, results from already available forced degradation studies were used, demonstrating that a decrease in API content higher than 10% could be expected. For LAMA, a significant degradation was observed under the abovementioned conditions, since the API completely degraded into two main degradation products. On the contrary, either long-acting β_2 agonist (LABA) or short-acting β_2 adrenergic agonist proved to be stable when tested at the currently employed washing conditions since the API degradation was below 3%. No significative mass balance gap was observed.

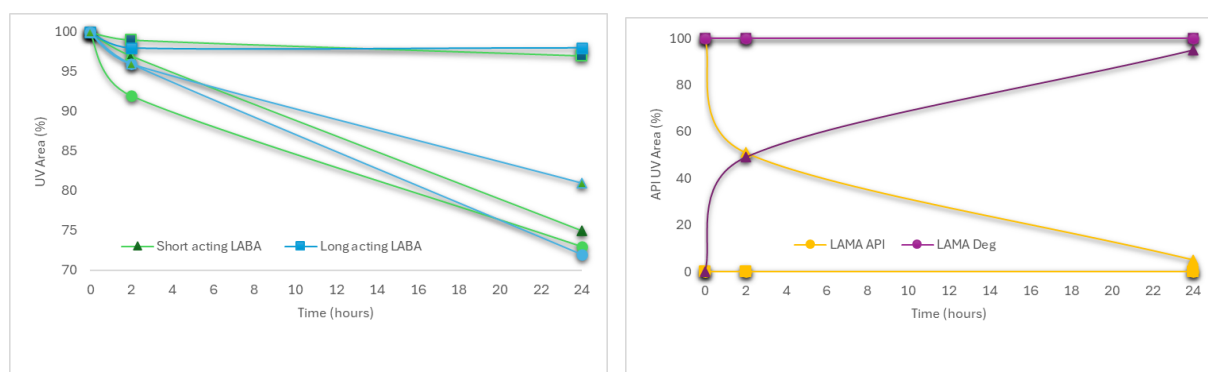


Figure 1 –APIs profiles up to 24 hours of exposure at different stressed conditions ■ (70°C, basic pH, 0.5% aqueous detergent), ● 40°C, basic pH, 0.5% aqueous detergent), ▲ (70°C, neutral pH, no aqueous detergent).

As preliminary phase to PiE, analysis of wastewater was conducted during manufacturing campaigns in order to determine the actual API concentration in the environment (PEC). Samples were collected during typical manufacturing campaigns and analyzed within 24 hours. Samples were collected either by means of a 24-hour autosampler, leading to a daily average of API content, or throughout one-off individual sampling. Preliminary post-production wastewater samplings focused on the quantification of the inhaled corticosteroid and related degradation products. It was observed that the amount of API and related degradation products discharged into the public sewerage system had fluctuating and non-reproducible values both within the same production campaign and over the periods evaluated. The introduction of a pilot system proved to be effective in guaranteeing the effectiveness of the API concentration abatement thus obtaining reproducible discharging values. In fact, neither API nor its degradation products were detected downstream of the pilot system.

Table 1 – PiE preliminary monitoring campaigns for inhaled corticosteroid active ingredient and its degradation product. Samples were collected in 3 consecutive days, one-off sampling each day. N.D. not detected.

Monitoring Campaign	Time (day)	Inhaled corticosteroid active ingredient (pg/mL)		Inhaled corticosteroid degradation product (pg/mL)	
		Pylot system input	Pylot system output	Pylot system input	Pylot system output
1	1	10	14	14571	4434
	2	<10	<10	80513	915
	3	34	10	72729	497
2	1	<10	<10	23690	173
	2	<10	15	15981	179
	3	<10	<10	23394	166
3	1	58	16	N.D.	N.D.
	2	27	<10	N.D.	N.D.
	3	14	<10	N.D.	N.D.

Table 2 – PiE preliminary monitoring campaigns for long-acting β 2 agonist (LABA), short-acting β 2 adrenergic agonist and LAMA (active ingredient and its degradation products). Samples were collected in 1 day as one-off sampling.

Active ingredient therapeutic class	Preliminary Monitoring Campaign 1 (pg/mL)		Preliminary Monitoring Campaign 2 (pg/mL)		Preliminary Monitoring Campaign 3 (pg/mL)	
	Pylot system input	Pylot system output	Pylot system input	Pylot system output	Pylot system input	Pylot system output
Short-acting β 2 adrenergic agonist	<10	<10	<10	<10	<10	<10
Long-acting β 2 agonist (LABA)	1374	184	88	17	51	<10
LAMA	<10	25	<10	<10	16	11
LAMA degradation product 1	N.D.	N.D.	103	<10	2750	75
LAMA degradation product 2	N.D.	N.D.	34	<10	3937	75

Hence, based on the concentrations detected in wastewater samples from PiE preliminary monitoring campaigns, for each API the experimental PEC was calculated considering any possible dilution factors from the final effluent discharge into the receiving environment. Taking into account the available data on ecotoxicological properties and the manufacturing discharges, by considering standard productions compared to long-term ecotoxicological effects, the risk was characterized in terms of the quotient PEC/PNEC. The risk quotient was calculated to be below 1. Therefore, an environmental risk derived from the discharge concentrations was deemed to be excluded.

Conclusion

The growing scientific attention regarding the presence of pharmaceuticals in the environment highlighted the importance of assessing potential environmental concerns in order to guarantee APIs safe discharge levels from the manufacturing plants. PiE aims at guaranteeing a responsible management of the manufacturing effluents and wastewaters. A tiered approach was pursued starting by collecting estimations of APIs release (PEC) from the manufacturing plant together with literature data evaluation. Subsequently, PNEC from ecotoxicological studies on aquatic wildlife were established. Stress tests showed that, under conditions that mimic the washing conditions of the manufacturing plant, some APIs rapidly degraded into related products, proving the importance of monitoring also degradation products trace water levels. Although the risk management process is intended as a continuous process by which Chiesi identifies hazards associated with APIs, estimates and evaluates the risks and monitors the effectiveness of the controls, results from this study showed that the ratio PEC/PNEC is below 1. Hence, Chiesi proved that the levels of its own drug products found in wastewaters are safe to the wildlife and environment. The present conclusions are based on reliable proprietary ecotoxicological data for derivation of PNEC and PiE preliminary sampling campaigns for chronic release verification and estimation of PEC with suitable analytical methods.

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