Pharmaceuticals in the Environment: Emerging Environmental Contaminants –

Approaches to Fate and Effects Testing of Active Pharmaceutical Ingredients

Allan W. Ader, Ph.D., DABT, Principal Toxicologist

The quantity of pharmaceuticals and personal care products (PPCPs) entering the environment each year is reported to be similar to the amounts of pesticides used each year (Daughton and Ternes, 1999). Some of the concerns are:

- Recent reports have verified that PPCPs are finding their way into the waterways. (see US Geological Survey report See http://pubs.acs.org/hotartcl/est/es011055j_rev.html)

- PPCPs enter the environment continuously via domestic and industrial sewage systems as opposed to pesticides that enter the environment seasonally;

- Many of these chemicals are very long-lived, many break down into other long-lived compounds and almost nothing is known about their movement in the environment. Even short-lived PPCPs can cause chronic exposures because they are continuously discharged into the environment;

- Most PPCPs have not been examined for adverse environmental effects. Many of these chemicals are designed to cause physiologic effects. Consequently an impact on aquatic and terrestrial organisms would not be surprising;

- Even though individual concentrations of any drug might be low, the combined concentrations from drugs sharing a common mechanism of action could be substantial.

Pharmaceutical and biotechnology companies developing new therapies need to be proactive and evaluate the potential impact of discharging wastewater containing active pharmaceutical ingredients to the local municipal wastewater treatment plant (WWTP) or to the downstream waterways. In addition, drug approvals, especially in Europe, are being impacted by the concern that use of these active pharmaceutical ingredients (APIs)

may adversely affect the environment, and the "threshold" for testing is at a much lower level than current US requirements.

I. Environmental Fate and Effects Studies

A cost-effective environmental fate and effects screening program for active pharmaceutical ingredients has been developed by **SafeBridge Consultants, Inc**. The purpose of this program is: 1) to respond to concerns regarding the potential environmental impact of discharging process wastewater containing active pharmaceutical compounds, and 2) to reduce the collection and off-site disposal of pharmaceutical containing wastewater which is very expensive.

The approach to testing would depend on whether the drug is an existing compound / product or a new chemical entity or active pharmaceutical, which would require a US New Drug Application (NDA) or application for approval in the EU from the EMEA. For older products, you would not need to conduct "definitive" studies that meet stricter requirements for submission of data to regulatory authorities such as FDA or EMEA, but could conduct "screening" evaluations of the same endpoints.

For both types of compounds (whether old or new) two assessments are needed:

1. Assessing toxic effects on aquatic organisms (Effects); and
2. Assessing the potential for biodegradation (in a waste water treatment plant) (Fate).

If you had an older drug where you do not have a concern over submitting data for later regulatory approval, "screening" tests recommended would include:

- Acute daphnia or fish testing (static) (acute aquatic LC or EC50) as a measure of acute toxicity on aquatic organisms; and
- Respirometer test, as a measure of biodegradation.
- Alternatively, **Microtox®**, a rapid, inexpensive aquatic bioassay useful for providing relative changes in toxicity, e.g. in a wastestream or collection tank effluent, which occur due to changes in the process or constituents. A good correlation between Microtox results and the 96-hour acute aquatic LC_{50} has been reported

Using these two tests you could estimate fate and effects of the chemical and these results can then be used to an acceptable discharge limit for the drug in the waste water of your facility.

If you had a new drug, "screening tests" are not adequate as, although good estimates of the effects and fate, they may not be "submittable" to the Agency as there are more specific requirements built into new regulations. In this case, we would recommend:

- Acute daphnia testing (static) but with analytical confirmation of the concentration throughout the study;

- A ready biodegradation study as part of the measure of biodegradation; and
- A respiratory inhibition study which would determine how the material behaves in a waste water treatment plant (some consideration could also be made to include it in the above (with an older compound).

As these studies may need to be submitted to the US or EU authorities, you may have to conduct them as GLP studies.

As with the “screening studies” these data can also be used to determine a disposal guideline based on the fundamental toxicological principles of acute aquatic toxicity, and biodegradability (environmental persistence).
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With either set of data, human health considerations are also needed to be assessed to determine an acceptable discharge concentration or approach. If you are employing an occupational categorization or banding system, environmental criteria and occupational criteria can be used to develop general guidelines based on occupational toxicity and potency and the environmental data (SafeBridge has developed some unique approaches for Clients in this regard).

The information is also useful for:
- A preliminary indication of the potential environmental impact from consumer use;
- Technology transfer;
- Augmenting the Material Safety Data Sheet (MSDS);
- Reducing regulatory burden; and,
- Potentially significant cost savings with regard to the responsible disposal of process wastewater; and for
- Environmental assessment requirements for new drug approvals, especially in the EU. In the competitive environment in which pharmaceutical and biotech companies find themselves today, a short "time to market" is a critical advantage. Deficiencies in the environmental assessment component of the FDA or EMEA submission can and have severely hampered the approval of a new drug product.

Furthermore, the growing awareness among the general public of pharmaceuticals as emerging environmental contaminants should encourage companies to proactively determine the potential impact of their products on the community.

Comments and questions can be directed to:
Allan W. Ader, Ph.D., DABT
SafeBridge Consultants, Inc.
1924 Old Middlefield Way
Mountain View, CA 94043-2503
Phone: (650) 961-4820 ext. 228
Fax: (650) 623-0096
allan.ader@safebridge.com