persistence and bioaccumulation and applying an increased number of alternate scenarios. Ecotoxicity screening involves estimation of the predicted no-effect concentration (PNEC) based on the results of long-term toxicity tests in fish, daphnia and algae. The PEC/PNEC thus obtained in Tier A determines whether a subsequent Tier B assessment would be conducted. Phase II Tier B involves further refined estimation of the PEC and an increased number of ecotoxicity tests, if required. The PEC/PNEC obtained at the end of Tier B determines whether the drug substance poses risk to the environment.

Table 1-2-2. Overview of the environmental risk assessment procedures for medical products for human use according to the EMEA guideline.

Stage	Assessment	Objective	Method	Test/Data Requirement
Phase I	Pre-screening	Estimation of exposure	Action limi	Consumption data, logKow
Phase II Tier A	Screening	Initial prediction of risk	PEC/PNEC	Base set aquatic toxicology and fate
Phase II Tier B	Extended	Substance and compartment-specific refinement and risk assessment PEC/PNEC	PEC/PNEC	Extended data set on emission, fate and effects

1-2-2. Domestic Trends

1) Veterinary Drugs

In Japan, veterinary drugs are controlled under the Pharmaceutical Affairs Law (regulating manufacture, marketing, and use of veterinary drugs), the Law concerning Safety Assurance and Quality Improvement of Feeds (Feed Safety Law) (regulating manufacture, marketing, and use of of feed additives), and the Food Sanitation Law (defining standards for quality and safety of foods).

The Pharmaceutical Affairs Law and Feed Safety Law define specifications for veterinary drugs used to feed livestock, poultry, and fish as well as standards on use thereof, while the Food Sanitation Law provides specifications and standards for food materials and end products produced from stock farm products and fishery products to control residual veterinary drugs therein. For marketing approval of veterinary drugs and quasi-drugs, submission of data specified in Table 1-2-2 is required. To date, no data on environmental impacts has been required for approval.

However, an international guideline for environmental impact assessment for veterinary drugs1-3) has already entered into force as of 2007, which requires amendment of current domestic regulations on application for approval of veterinary drugs to include environmental impact assessment as a part of toxicological testing.

Table 1-2-2. Data Required for Application for Approval of Veterinary Drugs in Japan as specified by The Regulations for the Control of Drugs, etc.

1	Drugs	2	Quasi-drugs
A	Origin or background of discovery, condition of use in foreign countries, etc.	A	Origin or discovery of drug, condition of use in foreign countries, etc.
B	Data on physicochemical and biological properties, standards, and test methods	B	Data on physicochemical and biological properties, standards, and test methods
C	Data on stability	C	Data on stability
D	Data on toxicity	D	Data on safety for target animals
E	Data on pharmacological action	E	Data on effectiveness or efficacy
F	Data on absorption, distribution, metabolism and excretion		
G	Data on results of clinical trials		
H	Data on residue study		

2) Drugs and Quasi-Drags for Human Use

In 2004, production of drugs for human use in Japan amounted to 6.5 trillion yen in total, and prescription drugs accounted for approximately 90% of the total production.[5)] Statistical data for the total amount of drugs produced are not available, but are provided for separate drug categories: cardiovascular agents, 167 tons (18 items); other metabolic agents, 3346 tons (8 items); central nervous system drugs, 1064 tons (15 items); gastrointestinal agents, 1935 tons (10 items); antibiotic agents, 0.5 tons (9 items); vitamin preparations, 10698 tons (15 items). Items belonging to each drug category include those that were not actually produced within 2004. Production of quasi-drugs amounted to 773 billion yen in total (corresponding to approximately 12% of that for drugs) and medicated cosmetics accounted for approximately 40% of the total production of quasi-drugs. For some of the drug categories surveyed, the total amount of production (in tons) changed drastically as compared with that in 2003.

1-3. Significance of Introduction of Environmental Impact Assessment for Pharmaceuticals in Japan

1-3-1. Overview of Examination System for Chemical Substances in Japan

New chemical substances to be manufactured in or imported into Japan are regulated as shown in Fig. 1-3-1 (a schematic summary of the regulation flow), depending on the total amount of annual production or import, properties, and harmfulness to human health and the environment. First, they are divided into three groups based on the total amount of annual production or import: 1) less than 1 ton (or used as intermediate to produce another chemical substance), 2) 1-10 tons, 3) more than 10 tons. Manufacture or import of chemicals falling

into the first group requires prior verification of information provided in the application form, but does not require further submission of test results on the persistence (degradability), bioaccumulation, long-term toxicity for humans or ecotoxicity. For those belonging to the second group, submission of test results on persistence and bioaccumulation is mandatory, but data on risk to human health and the environment are optional. For chemical substances of the third group, submission of all test results specified is mandatory. After examination of the submitted data, chemical substances are classified on the basis of their properties and harmfulness to human health and the environment so as to be regulated differently thereafter as required:

Class I Specified Chemical Substance (manufacture and/or import virtually prohibited)
Class II Specified Chemical Substance (causes a risk to human health or the environment)
Type I Monitored Chemical Substance (to be subjected to monitoring together with existing chemical substances. Can be potentially classified as Class I Specified Chemical Substance depending on the results of further monitoring)
Type II Monitored Chemical Substance (possesses potential risk to human health)
Type III Monitored Chemical Substance (possesses potential to cause ecotoxicity)

Ecotoxicity is evaluated first by acute toxicity tests in algae, daphnia, and fish for screening purposes. For Type III Monitored Chemical Substances identified by screening, additional environmental risk assessment involving chronic toxicity tests in algae, daphnia, fish, and bloodworms is directed by the regulatory authority. Of the no-observed-effect concentrations (NOECs) observed in different test species, the lowest is used to estimate the predicted no-effect concentration (PNEC) for comparison with the predicted environmental concentration (PEC). For Type I Monitored Chemical Substances, chronic toxicity tests in top predators (e.g., birds) are directed by the regulatory authority to identify Class I Specified Chemical Substances.

1-3-2. Overview of Examination System for Pharmaceuticals in Japan

Manufacture, import, and marketing of new pharmaceuticals in Japan requires application for approval from the Ministry of the Health, Labour and Welfare with submission of a written application with the data specified in Table 1-3-1 attached to it. The submitted application documents are then examined for compliance with the Ministerial Ordinance on Standards for Practice of Nonclinical Studies on the Safety of Drugs (MHW Ordinance No. 21: GLP dated March 26, 1997), the Ministerial Ordinance on Standards for Practice of Clinical Trials (MHW Ordinance No. 28, GCP dated March 27, 1997, partially revised by MHLW Ordinance No. 106 dated June 12, 2003, MHLW Ordinance No. 172 dated December 21, 2004, and MHLW Ordinance No. 72 dated March 31, 2006), and the Criteria for

Reliability of Application Data (Article 43 of the Enforcement Regulations, Pharmaceutical Affairs Law) ("Reliability Criteria"). As indicated in Table 1-3-1, data currently required for approval application do not include those on environmental impacts and, as a consequence, the current examination criteria for approval application do not include the data on the impacts of the new pharmaceuticals to be examined on the environmental organisms and ecosystem.

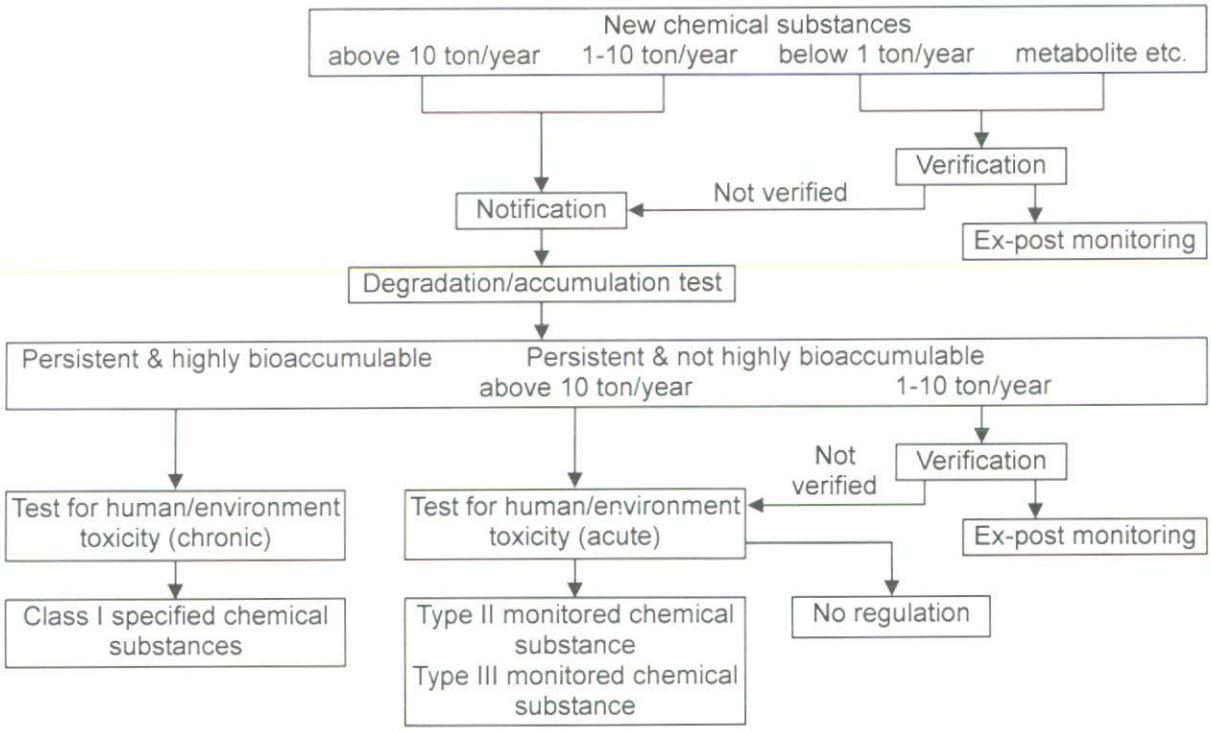


Fig.1-3-1. Overview of examination and control process for new chemical substances in Japan

Indicates the main flow, excluding "Existing chemical substance", "Type I monitored chemical substances", and "Class II specified chemical substances" for simplification.

Table 1-3-1. Data to be attached to the application for approval of new pharmaceuticals (as specified by Article 40, paragraph 1 of Enforcement Regulations of Phrmaceutical Affairs Law)

	Item	Data
A	Origin or discovery of drug, condition of use in foreign countries, etc	1 Origin or discovery of drug 2 Condition of use in foreign countries 3 Special characteristics, comparisons with other drugs, etc
B	Data on method for manufacture and data on specification and test methods, etc.	1 Determination of structure and physicochemical properties 2 Method for manufacture 3 Specification and test methods
C	Stability	1 Long-term storage tests 2 Stress stability tests 3 Accelerated stability tests
D	Pharmacological action	1 Tests to support efficacy 2 Secondary pharmacology, safety pharmacology 3 Other pharmacology
E	Absorption, distribution, metabolism, and excretion	1 Absorption 2 Distribution 3 Metabolism 4 Excretion 5 Bioequivalence 6 Other pharmacokinetics
F	Acute, subacute, and chronic toxicity, teratogenicity, and other types of toxicity	1 Single dose toxicity 2 Repeated dose toxicity 3 Genotoxicity 4 Carcinogenicity 5 Reproductive toxicity 6 Local irritation 7 Other toxicity
G	Clinical studies	Clinical trial results

1-3-3. Reports of Pharmaceuticals Detected in the Aquatic Environment in Japan

Tanqka et al.[6] simultaneously investigated 114 pharmaceuticals for human and veterinary use released into river water. They demonstrated that, of the pharmaceuticals investigated, 97 could be assayed simultaneously and 90 could be analyzed simultaneously by a single LC-MS/MS procedure. Using this method, they further selected 75 target compounds and deteremined their contents in river water and effluents from wastewater treatment plants collected at sampling points in the Yodo River Basin and Tone River Basin. In the Yodo River Basin, a total of 56 pharmaceuticals were detected and effluents from wastewater treatment plants tended to contain a greater number of pharmaceuticals (20 to 51 per sampling point) at higher concentrations as compared with those in river water. Different pharmaceuticals were detected at varying concentrations and the highest concentration exceeded 1000 ng/L. In the Tone River Basin, 72 pharmaceuticals were analyzed as target compounds. Fifty-three of these were also detected in river water samples (0.1-500 ng/L) and sixty of these in effluents from wastewater treatment plants (0.7-1350ng/L). The concentration in effluents from wastewater treatment plants did not exceed 100 ng/L for any, except 10, of the target compounds.

Kunikane et al.[7] investigated the experimental conditions for instrumental analysis of bioactive substances (pharmaceuticals) to assess uptake of pharmaceuticals from tap water into the human body and successfully established analytical conditions for 81 of the substances. Using their method, river water samples collected in the Tama River Basin were analyzed. While no pharmaceuticals were detectable in the upper Tama River, 35 pharmaceuticals were detected in the middle Tama River Basin receiving effluents from wastewater treatment plants. Although the observed maximum concentration exceeded 500 ng/L for some of the pharmaceuticals analyzed, the maximum annual median concentration (for 30 measurements obtained in one year) was 200 ng/L. Similar analyses for 18 pharmaceuticals conducted in the Sagami River Basin identified three chemicals at concentrations ranging from 2.1 to 56 ng/L. Also, a survey targeting 21 pharmaceuticals conducted at the Tone River Basin detected 10 to 11 of the chemicals (depending on the season) at a maximum concentration of 557 ng/L.

When influents and effluents of 8 wastewater treatment plants located in the Sumida River Basin and Ara River Basin were analyzed for 11 pharmaceuticals, all of the 11 were detected in the influent water samples and 10 in the effluent water samples. The observed maximum concentrations in the influent and effluent samples were 2774 ng/L and 5952 ng/L, respectively. Similarly, influents and effluents of 6 wastewater treatment plants located in the Sumida River Basin were analyzed 3 times during consecutive 2 years. The number of target compounds assayed in each survay was 81, 11 and 15, respectively. The first survey detected 33 and 31 of the 81 target pharmaceuticals in the influent and effluent samples, respectively, while the second and third surveys conducted for a reduced number of target pharmaceuticals identified all of these in both influent and effluent samples. The observed maximum concentration in the influent and effluent samples was 16850 ng/L and 1209 ng/L, respectively. In addition, wastewater samples from 3 hospitals were analyzed for 19 pharmaceuticals and 10 of the were identified at a maximum concentration of 11000 ng/L.

These reports demonstrate that development of innovative analytical technology has realized detection of pharmaceuticals from river water as well as in influents and effluents of wastewater treatment plants, the results suggesting that considerations on the environmental impact of pharmaceuticals are urgently needed.

1-3-4. Necessity of Introduction of Environmental Impact Assessment for Pharmaceuticals

As discussed above, protection of the environment (including both organisms and their habitats) in addition to protection of human health has grown into a key concept that is emphasized and necessary for establishing and implementing systems for examination and

regulation of chemical substances. Today, all chemical substances except pharmaceuticals are subjected to a variety of regulatory measures developed based on a common recognition of the importance of appropriate risk management based on any kind of risk assessment. Since pharmaceutials are originally intended to have biological activities, their environmental impacts are inevitable and may not always be ignorable. In addition, detection of pharmaceuticals in aqueous environments has been reported frequently in Japan and introduction of a management system for environmental risks posed by pharmaceuticals is urgently needed. These circumstances constitute the basis for extending the scope of environmental assessment and risk management systems from chemical substances to pharmaceuticals.

1-4. Summary

(1) Environmental impact assessment for chemical substances:

- Harmonized international guidelines have been developed and adopted by many countries, involving amendments of existing domestic systems if required.
- Usually involves stepwise assessment procedures (Teir and Trigger approaches).
- Requires acute toxicity test results in algae, Daphnia, and fish in most cases as basic data.
- Covers agricultural chemicals and veterinary drugs by developing specific measures taking into consideration the features of individual products (including usage).

(2) Environmental impact assessment for pharmaceuticals:

- Necessity of environmental risk assessment has been argued to trigger international movements towards regulation.
- Pharmaceuticals are biologically active and their impacts on the ecosysytem are inevitable when they are released into the environment.
- Chronic toxicity test results in algae, Daphnia, and fish have been proposed as requirements as basic data.
- Basically conducted as risk assessment (not as hazard assessment) based on the PEC/PNEC value.
- Detection of pharmaceuticals from aqueous environments, including river, water has been frequently reported.
- Movements towards regulation has started subsequently to those for other chemical substances and existing assessment procedures for such chemical substances provide good reference for developing regulatory measures

Section 2. Framework of Environmental Risk Management for Pharmaceuticals

2-1. Subject Matters

The present report exclusively deals with pharmaceuticals for human use, which are hereafter simply referred to as "pharmaceuticals" or "drugs".

2-1-1. Scope of the Subject Matters

Pharmaceuticals for human use include herbal medicinal products prepared from natural materials (mainly medicinal plants). Of such herbal medicinal products, those generally containing only limited amounts of active ingredients and used at limited doses are exempted from the environmental risk management proposed in the present report. However, if the active ingredients are extracted or purified from particular natural materials and are used to prepare pharmaceutical products, such active ingredients should be subjected to environmental risk management.

Diagnostic products have a potential for emission into the environment. However,since they generally contain only low amounts of bioactive constituents and are used almost exclusively at medical institutions such as hospitals and clinics, their emission into the environment can be and should be controlled by regulatory measures other than those generally applied to pharmaceuticals (e.g., inclusion in the scope of ordinary effluent regulation would be appropriate). Accordingly, they are tentatively exempted from environmental risk management proposed in the present report (See also Section 2-1-5).

Hormone preparations are tentatively excluded from the scope of management based on the impacts of their hormonal actions, because no testing methods for assessing the environmental impacts of biologically active ingredients of drug preparations that exhibit their effects at extremely low concentrations have been established as yet. Inclusion of hormone preparations in the scope of environmental risk management will be reconsidered in the future, taking into account the progress in the improvement of the prerequisite conditions for successful and effective management. This does not mean that hormone preparations will also be exempted from environmental impact assessment.

Narcotics are exempted from the environmental risk management proposed in this report, because they as used for limited purposes at limited sites.

Genetically modified organisms are controlled in accordance with The Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Cartagena Law, effective 2004): prior environmental impact

assessment is required for their cultivation as crops, with their cultivation sites restricted, and prevention of their diffusion into the environment is required. The safety of food, food materials, and food additives produced by application of genetically modified organisms are regulated by The Guideline for the Safety Assessment of Foods and Food Additives Produced by Recombinant DNA Techniques (1991). However, discussion of the ecotoxicity of substances extracted from or secreted by genetically modified organisms is beyond the scope of this Guideline. Genetically modified organisms themselves, or their constituent biological macromolecules (peptides, carbohydrates, lipids, etc.), are not pharmaceuticals, and are therefore excluded from the scope of the environmental risk management proposed in the present report. However, if particular substances extracted from or secreted by genetically modified organisms are used as active ingredients of pharmaceuticals, these woukd be subject to the environmental risk management proposed in the present report.

Nutrients such as vitamins, electrolytes and amino acids are excluded from the scope of environmental risk management proposed in the present report, because these substances in medicinal products emitted into the environment are expected to be much smaller in amount compared with that in other products such as food, limiting their impact to a limited area.

Based on the concepts described above, all pharmaceuticals for human use, except for herbal medicinal products, diagnostic products, biological macromolecules, vitamins, electrolytes and amino acids are subject to environmental risk management proposed in the present report. It should be noted that the actual subjects of this risk management are drug substances used as active ingredients (not individual drug preparations as final products). In other words, if two different products A and B contain an identical active ingredient X, environmental risk management is conducted for X only.

2-1-2. Concepts on Drug Metabolites

After administration, a portion of the active ingredient of a drug is metabolized and converted to metabolite(s) during transfer within the human body. In some cases, the drug substance has only a limited physiological activity immediately after administration (pro-drug), but is metabolized in vivo to generate a metabolite that exhibits a strong physiological activity as intended. The unchanged drug and/or its metabolite(s) (including conjugates of a polar molecule) are excreted and enter the environment. Some of these unchanged drugs and/or its metabolite(s) (designated hereafter as "drug metabolites etc.") substances may be further metabolized by organisms in the environment. Conjugates may be cleaved by microorganisms during wastewater treatment processes to regenerate the unchanged drug.

Considering the complex pharmacodynamics of a drug after administration outlined

above, it may be inapropriate to include drug metabolites generated in the human body in subjects of preliminary or initial risk assessment, because this may make the assessment process even more complicated. Therefore, preliminary risk assessment should be basically conducted for unchanged drug substances (and also for activated drugs in the case of pro-drugs). Metabolites may be taken into consideration in subsequent phases of the assessment.

2-1-3. Concepts on Readily Degradable or Degradation-Resistant Substances

Pharmaceuticals may be either degraded biologically (biodegradation) or decomposed non-biologically (via physicochemical processes such as hydrolysis and photolysis) to be converted to carbon dioxide, carbon, water and ammonia (mineralization), or an organic compound with a chemical structure different from that of the unchanged drug. If the drug metabolite etc., to be assessed is completely degraded/decomposed and mineralized via a biological or non-biological processes, no risk of exposure is expected thereafter and this substance may well be excluded from subsequent steps of assessment. Thus, it would be reasonable to require the applicant to conduct a biodegradation test and stability test for the drug to be examined and submit the data on the biodegradability and stability of the substance, as well as information on its degradation products, as required for common chemical substances by Chemical Substances Control Law. Data on other parameters essential for environmental risk assessment (water solubility, octanol/water partition coefficient) should also be submitted whenever possible.

2-1-4. Concepts on Substances Highly Susceptible to Bioconcentration

Taking bioaccumulation through the food chain into consideration, susceptibility to bioconcentration is an important factor that would determine the environmental risk of a particular drug. Once a drug is found to be highly persistent (resistant to degradation), it should be tested for bioaccumulation as well. While susceptibility to bioconcentration is generally judged from test results for stability, biodegradability, water solubility, and bioaccumulation, as well as from the octanol/water partition coefficient, it would be most reasonable to apply the test method and criteria for bioaccumulation specified by the Chemical Substances Control Law correspondingly to drugs. Among drugs discharged into the environment, those that are highly suseptible to bioconcentration should be subjected to more strict control than others, as is the case with common chemical substances.

2-1-5. Effluent Regulation

Some drugs, such as diagnostic products, may be discharged at high concentrations or in

high amounts into the environment of a particular area and should be most effectively and economically controlled by applying general regulatory measures for effluents. Besides high-volume emission from facilities using drugs, high-volume emission from facilities manufacturing drugs should also be controlled similarly.

For example, iodinated X -ray contrast agents are used in the largest amounts at a small number of facilities capable of high-level medical treatment (major general hospitals, surgical facilities) and emission from such facilities are expected to be account for the most part of the burden of absorbable organic halogen compounds in the aquatic environment. For some special substances used at a limited number of special sites, such as gadolinium (Gd) used in magnetic resonance imaging (MRI) examination and cytostatic agents used for cancer chemotherapy, the exact amount of each drug used can be figured out.

However, controlling emission of a particular drug separately by developing regulation measures dedicated to it may be difficult and even impractical. Rather, application of a comprehensive regulation for effluents containing multiple toxic substances by conducting the Total Effluent Toxicity Test (an ecotoxicity test using effluents as test samples) would be more efficient. Such regulatory measure would raise environmental consciousness of personells working at facilities responsible for high-volume emission of drugs and trigger introduction of an advanced effluent treatment such as batchwise treatment at higher drug concentration.

2-1-6. Exceptional Measure for Existing Pharmaceuticals

For existing pharmaceuticals, few cases of serious environmental impact are known. Therefore, it would be possible to approve continuation of their production with a certain limit placed on the amount produced (or used). To produce them in an amount exceeding this limit, prior environmental impact assessment should be required, as is the case with production of new pharmaceuticals. Upon application of such an exceptional measure to existing pharmaceuticals, it would be appropriate to grant a delay for a definite period prior to uniform application of regulatory procedures for new pharmaceuticals, in view of comprehensive environmental impact management for chemical substances as the ultimate goal of their regulation.

2-2. Special Factors to be Considered in the Assessment Process

There are many alternative approaches used for environmental impact assessment and one of them is finally selected for application to the actual assessment process. The reason(s) for selecting one particular approach from among multiple alternatives should be clearly explained in developing the assessment procedure and reporting the assessment results. This section describes some basic approaches currently used for environmental impact

assessment, with modifications to cope with a varitery of different circumstances, also referring to some special factors to be considered in selecting the approach to be used.

2-2-1. Assessment using PEC/PNEC

The ratio of predicted environmental concentration to predicted no-effect concentration (PEC/PNEC ratio) is the parameter that is generally used as an index of environmental impacts. Adverse effects of a target substance on the ecosystem become a concern when the PEC exceeds the PNEC (the concentration at which no adverse effects is expected based on experimental data). This approach is internationally adopted due to the clear, simple and easy-to-understand underlying concept.

On the other hand, environmental impact assessment based on the PEC/PNEC ratio has the disadvantage that the values of PEC and PNEC do not always reflect the dynamics of the target substance in the actual environment. This is because both of these parameters are calculated on the basis of one particular set of conditions and are therefore incapable of reflecting any change in the pattern of toxic effects or the time-dependent and/or spatial changes in the environmental conditions such as variations in the river flow rate. Thus, assumptions employed in the calculation of PEC and PNEC should be carefully considered while interpreting the results. For example, the ratio for dilution of effluents by river water depends on the value of the river flow rate that cannot be controlled artificially. Accordingly, the calculated value of each parameter may vary depending on the river flow rate used for the calculation (mean, 90th percentile, or 50th percentile). An assessment procedure using PEC that takes this limitation into account is therefore needed.

2-2-2. Assessment Using PEC/PNEC Derived from a Probabilistic Approach

Besides environmental impact assessment using the classical PEC/PNEC, alternative approaches are available, including the following: 1) approaches considering dose-response relationships; 2) approaches considering variations in both exposure and effects; 3) approaches involving process model construction; 4) empirical approaches involving field tests.

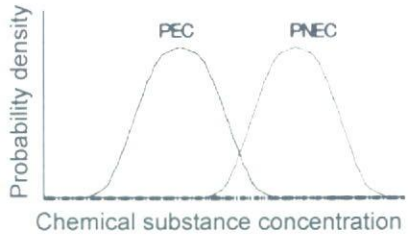
1) Approaches considering dose-response relationships

Approaches of this type assume a constant PEC and take a variations of the PNEC into consideration by applying a probabilistic approach. One such approach does not use the observed raw value for LC_{50} or NOEC in the calculation of PNEC, but uses probability distribution for these parameters representing ecotoxic effects. A probability distribution of PNEC, calculated by assuming that the dose-response relationship found in acute toxicity

studies is applicable to chronic toxicity studies as well, is used to estimate a probability that the PNEC value falls below the PEC. Alternatively, when multiple sets of chronic toxicity data are available, the probability distribution of PNEC is calculated by assuming that the obtained data fit a logarithmic normal distribution function to estimate the probability that the PEC/PNEC ratio exceeds 1. The resulting exceedance probability values are compared with a predefined reference value to determine if the target substance has ecotoxicity.

2) Approaches considering variations in both expsure and effects

In the actual environment, both the sensitivity of organisms to ecotoxicity of the target substance and the exposure concentration of the same substance may vary. More elaborate approaches for environmental impact assessment using the PEC/PNEC ratio considers variation of both of these factors in the calculation of PEC and PNEC. The resulting exceedance probability value is then compared with a predefined reference value as in 1). The figure at the right schematically represents the basic concept of these approaches.



3) Approaches involving process model construction

While the approaches described in 1) and 2) can be used to estimate ecotoxicity only in a small number of test species, environmental impact assessment using a process model estimates how environmental impacts on one species may further affect other co-existing species as well as the surrounding environment itself, by constructing a model for simulation. Such approaches have an advantage that impacts under conditions that are impossible to realize in the actual laboratory or field testing (e.g., higher concentrations, longer assessment period, larger area of the assessment field) can be investigated using the constructed model. Although there is no doubt that approaches of this kind are the closest to the ideal, it should be noted that scientific justification is essential for constructing and adopting a mathematical model. A model constructed to simulate environmental impact of one chemical substance and successfully explaining the experimental data obtained may not always be applicable to another substance as well. A simulation model is possible with subjects or situations that are known to some extent, but is difficult to extrapolate to other subjects/substances/situations?.

4) Empirical approaches involving field studies

Approaches of this kind involve exposure studies conducted in the outdoor field and allow most accurate estimation of environmental impacts. However, it should be noted that

long-term field studies are costly and there is the concern of overlooking impacts not included in the endpoints of the study.

2-2-3. Exempted Items

The term "exempted items" refers to pharmaceuticals (drugs) for which no environmental risk asssessment is required, because it appears inappropriate to include them as subjects of environmental risk management proposed in this report. As already described in Section 2-1-1, herbal medicinal products, diagnostic products, biological macromolecules, vitamins, electrolytes and amino acids are excluded. In addition, active ingredients of pharmaceuticals also occurring in nature at considerable concentrations are excluded as well.

Of pharmaceuticals as well as their active ingredients and synthetic intermediates, substances falling into such categories as "intermediates", "substances exclusively exported", and "substances exclusively used in a closed system" defined by The Chemical Substances Control Law should be handled as follows:

1) Intermediates should be handled as common chemical substances, not as pharmaceuticals.

2) Substances exclusively exported should be exempted from the present risk management, as well as from environmental impact assessment required by The Chemical Substances Control Law. Although it is desirable that systems required for environmental assessment are already in place in the country importing these substances, such systems need not be defined as an essential requirement for importing them, considering the fact that they are intended to be used as pharmaceuticals.

3) Substances exclusively used in a closed system should be exempted from the present risk management, although few such substances might exist. This does not mean that pharmaceuticals exclusively used in a particular ward should be handled as "substances exclusively used in a closed system".

There might be cases of some pharmaceuticals essential to human life and in public interest have a potential risk of environmental impacts. Whether or not application of exceptional regulatory measures to such pharmaceuticals is valid should be carefully decided on a case-by-case basis, which would require development of a separate assessment system that would provide procedures and criteria for such a decision.

2-2-4. Stepwise Assessment Procedures

Environmental impact assessment of chemical substances require data that constitute the basis of judgement on whether or not the target substance has ecotoxicity. More complicated studies conducted for longer periods could yield more elaborate data, but at a higher cost because of the prolonged study period as well as a greater complexity of the study

design. Accordingly, social consensus should be achieved on which level (or what kind) of ecotoxicity study is required for a given pharmaceutical.

Stepwise procedures are internationally adopted for environmental impact assessment, in order to improve assessment efficiency and ensure safety. Since the assessment cost greatly varies depending on the level of study required at a particular step in the assessment process, key points in developing a stepwise assessment procedure are to properly stratify the levels of data collection applied to different steps in the assessment model adopted, and to define clear criteria for moving on to a higher level of assessment.

Simple and easy screening tests are required at the initial or preliminary step of the assessment process. For pharmaceuticals found to have only a minor environmental risk at this screening step, no further testing should be required. At the subsequent steps for higher levels of assessment, more elaborate toxicity studies are required to obtain more detailed data on the findings obtained at the initial screening step. The total number of different steps in a particular assessment procedure would vary depending on the assessment model used to develop the procedure, as is obvious from the following examples.

Environmental risk management according to the EMEA guideline[1)] actually involves three different steps. At the first step, the possibility of exposure to the target substance (PEC) is the sole parameter required for preliminary assessment. The second and third steps involve assessment based on the PEC/PNEC ratio. At the second step, PNEC is estimated using long-term toxicity values and activated sludge respiration inhibition test results (obtained for substances exhibiting antibacterial action). At the third step, a more elaborate PNEC value is estimated by further considering sale forecast data for the product containing the target substance as the active ingredient, adsorption coefficient for the target substance, and characteristics of the assessment area. Metabolites are also included in the subjects of assessment at this final step. PNEC is derived from the data obtained in the ecotoxicity tests of the sediments, terrestrial environment and microorganisms. The EMEA guideline points out that estimating PNEC based on short-term (acute) toxicity data is not appropriate for environmental impact assessment of pharmaceuticals intended for continuous use.

In Japan, environmental impact assessment for common chemical substances according to The Chemical Substances Control Law apparently involves four different steps: the first step, preliminary examination of the possibility of exposure (conducted for new chemical substances that fall into the category of "low-volume production chemicals") based solely on PEC; the second step, assessment of susceptibility to biodegradation and bioconcentration (for Type I Monitored Chemical Substances); the third step, assessment based on the results of acute toxicity tests for screening (to identify Type III Monitored Chemical Substances); fourth step, assessment based on chronic toxicity test results as well as the estimated

exposure level (conducted for Type III Monitored Chemical Substances to identify Class I and Class II Specified Chemical Substances).

On the other hand, assessment of the environmental impacts of agricultural chemicals used in rice paddies on aquatic organisms according to The Agricultural Chemicals Regulation Law requires estimation of a single PNEC solely based on acute toxicity test results, while the PEC is estimated at three different steps in the assessment procedure using different parameters representing the amount of runoff from the field and refined to varying extents (the first step uses predefined figures, the second step uses the values estimated by conducting a water contamination test in the assessment field, and the third step uses actual concentration of the target substance in water determined for an actual rice paddy).

Thus, it can be easily understood that the total number of steps in the assessment procedure and criteria for moving on to a subsequent assessment step for more elaborate examination depends greatly on the assessment model adopted. Also, it should be understood that development of a stepwise assessment procedure also depends on the level of assessment technology currently feasible. Anyway, it may be beneficial to adopt an appropriately developed stepwise procedure for environmental impact assessment of pharmaceuticals.

2-2-5. Categorization (Grouping) of Target Substances

Categorization (or grouping) of chemical substances to be tested for toxicity allows a rough estimation of the toxicity data for substances whose toxicity is unknown to date from the data available for other related substances with known toxicity belonging to the same category. This section discusses whether categorization of target substances is appropriate or helpful in estimating and assessing the ecotoxicity of pharmaceuticals.

There are very few cases in which categorization of the target substances facilitate estimation of the toxicity of pharmaceuticals. Actually, the demands for toxicity estimation based on categorization of target substances are minor at present, because few ecotoxicity test results have been accumulated to date for pharmaceuticals, and also because the total number of pharmaceuticals is smaller compared with that of common chemical substances (which leaves development of an assessment model as a task for the future, based on the expectation that the necessary test data will be made available in the future). Nevertheless, there still remains the possibility that the concept of categorization might be introduced into toxicity estimation for particular substances, such as drug metaoblites. Accordingly, the possibility of toxicity estimation after categorization of target substances cannot be ruled out and responses to a proposition of its introduction should be taken into consideration, depending on the situation for each target substance.

For different pharmaceuticals with identical (or at least simmilar) points of action or mechanism of action, it may be difficult to assure ecological safety by controlling each of such pharmaceuticals separately. Additive and/or synergistic actions of such multiple pharmaceuticals may cause adverse effects on environmental organisms. Accordingly, introduction of an environmental impact assessment method based on a predicted total sum of emissions for such groups of pharmaceuticals might be effective. However, it is not easy to classify all pharmaceuticals into categories based on the points or mechanisms of actions in environmental organisms and then to confirm an additive and/or synergistoic action of such multiple pharmaceuticals. Furthermore, there is no evidence to support the possibility that pharmaceuticals divided into one category on the basis of their mechanisms of action in the human body would also fall in the same category when the categorization is based on their environmental impacts. On the other hand, categorization of antibacterials on the basis of the lowest- observed- effect- level might facilitate assessment of their environmental impacts. Considering these circumstances, environmental impact assessment of pharmaceuticals after categorization should not be adopted at present, but should be left for further discussion to reach a final decision in the future.

2-2-6. Total volume control

Categorization of pharmaceuticals for environmental risk assessment discussed in 2-2-5 may be extrapolated to the concept of total volume control. Assuming that the total water flow in water systems in Japan (including rivers, lakes, etc.) is constant over time, it is difficult to protect the ecosystem against the environmental impacts of a drastic increase in number of pharmaceuticals simply by controlling each of them separately. To avoid such a situation, total volume control considering the total environmental risk posed by emission of all pharmaceuticals in Japan may be a countermeasure to be considered. Actually, however, environmental damage are not caused by pharmaceuticals alone and the contribution of common chemical substances other than pharmaceuticals may be expected to be greater than that of pharmaceuticals. Accordingly, application of a total volume control system developed exclusively for pharmaceuticals is not likely to function as a practical countermeasure. If total volume control is to be applied to pharmaceuticals, their inclusion in the subjects of a total volume control system for all chemical substances would be the most appropriate solution. In other words, it is neither logical nor reasonable to control pharmaceuticals separately from other chemical substances. Environmental impact simulation to separately evaluate the magnitude of the environmental risk posed by pharmaceuticals and all chemical substances for comparison would be worth while in a debate on total volume control.

2-3. Concept Underlying the Proposed Envitonmental Impact Assessment Method

Figure 2-3-1 schematically illustrates a general risk assessment/management system. In this system, the final decision is derived from risk-benefit assessment, an appraoch for decision-making unconsciously accepted in our daily life.

Environmental risk assessment proposed in the present report basically follows the general assessment strategy summarized in the figure. Risk-benefit assessment has seldom been adopted explicitly as a decision-making strategy in the conventional assessment process for the following two reasons: 1) the technical criteria for judgement in risk-benefit assessment are difficult to establish and have often been defined on a case-by-base basis; and 2) existence of certain benefit(s) is assumed as a prerequisite for management. Considering that pharmaceuticals are essential to human life and are in public interest, but the situation surrounding each product may vary, risk-benefit assessment should be explicitly adopted in environmental risk assessment of pharmaceuticals.

The environmental risk for each product should be assessed on the basis of the PEC/PNEC ratio. Environmental risk assessment proposed in the present report does not include the process of risk management shown in Fig. 2-3-1. Also, examination of individual risk characterization factors is beyond the scope of the proposed risk assessment, because this process is assumed to be already complete during development of the assessment system. Consequently, exposure assessment and effects assessment constitute the major part of environmental risk assessment proposed in the present report and the most important technical task in this assessment is to establish procedures for estimating the PEC and PNEC. Detailed stepwise procedures for estimating these parameters are described in the subsequent sections.

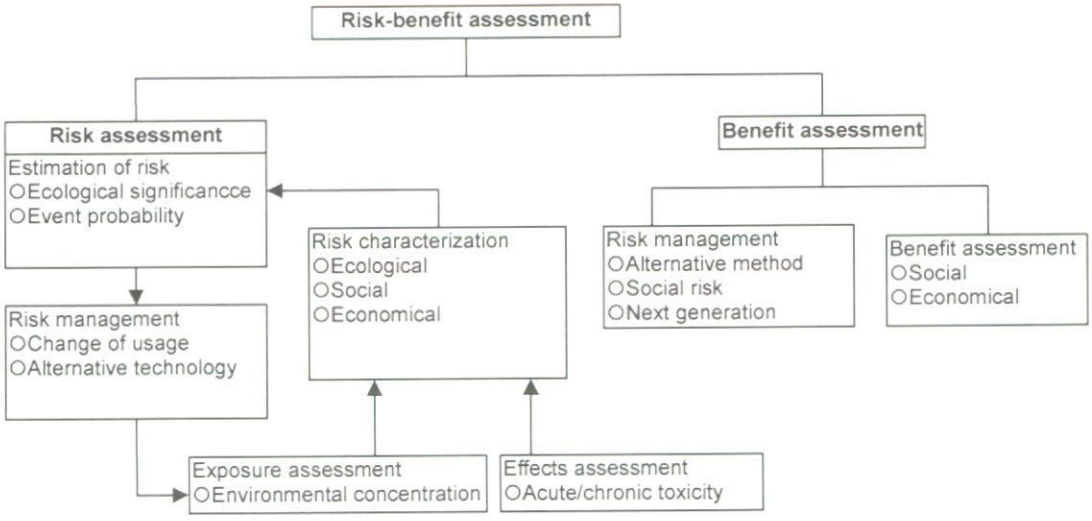


Fig. 2-3-1. A general risk assessment/management system

2-4. Summary

An environmental impact assessment system applied to pharmaceuticals for human use should be constructed based on the following principles:

- Scope of the subject matters

1) All pharmaceuticals for human use, except for herbal medicinal products, diagnostic products (exclusively used in facilities , biological macromolecules, vitamins, electrolytes and amino acids are subjected to environmental risk management proposed in the present report.
2) Pharmaceuticals exclusively exported as well as those exclusively used in a closed system may be exempted.
3) Continuation of production of existing pharmaceuticals should be approved with a certain limit placed on the amount produced (or used). Upon application of such an exceptional measure to existing pharmaceuticals, it would be appropriate to grant a delay for a definite period prior to uniform application of regulatory procedures for new pharmaceuticals.
4) Individual drug substances used as active ingredients shall be subject to this risk management. Initial or preliminary risk assessment should be conducted for unchanged drug substances (and also for activated drugs in the case of pro-drugs), while metabolites should be considered at subsequent steps of the assessment.

- Assessment system

5) Involves a stepwise assessment procedure.
6) Possibility of toxicity estimation after categorization of target substances should not be ruled out completely. Environmental impact assessment of pharmaceuticals after categorization should not be adopted at present.
7) Involves risk-benefit assessment for the final decision.
8) Readily degradable pharmaceuticals are exempt from submission of data on bioconcentration and ecotoxicity.
9) Substances highly susceptible to bioaccumulation should be subject to more strict control than others.
10) The environmental risk is assessed on the basis of the PEC/PNEC ratio.

Section 3. Estimation of Environmental Concentration

This section describes the method for estimating the predicted environmental concentration (PEC) to be adopted in Japan. The present study investigated a method for calculation of the $PEC_{surface}$ water in river surface water (partly considering groundwater). The method was investigated in a stepwise manner for the following 3 different levels: LEVEL 1, basic PEC estimation for screening and general purpose (to be compared with the reference level); LEVEL 2, estimation of PEC considering more specific situations (e.g., for a particular environmental compartment, for a smaller assessment area, etc.); and LEVEL 3, refined (or elaborate) estimation of PEC (with metabolites included in the emission scenario).

3-1. Emission Scenario Used and Basic Principles of PEC Estimation

Used or unused pharmaceuticals that had been prescribed to patients are excreted from the human body and then flow into public water areas via wastewater treatment plants and/or digestion tanks. Also, unused pharmaceuticals are burnt or landfilled as wastes. Pharmaceuticals directly landfilled or adsorbed onto sewage sludge for subsequent landfill into a waste disposal site may leak into the external environment as pollutants, making garbage landfills potential sites of environmental pollution. These routes of emission of pharmaceuticals into the environment are summarized in Fig. 3-1-1.

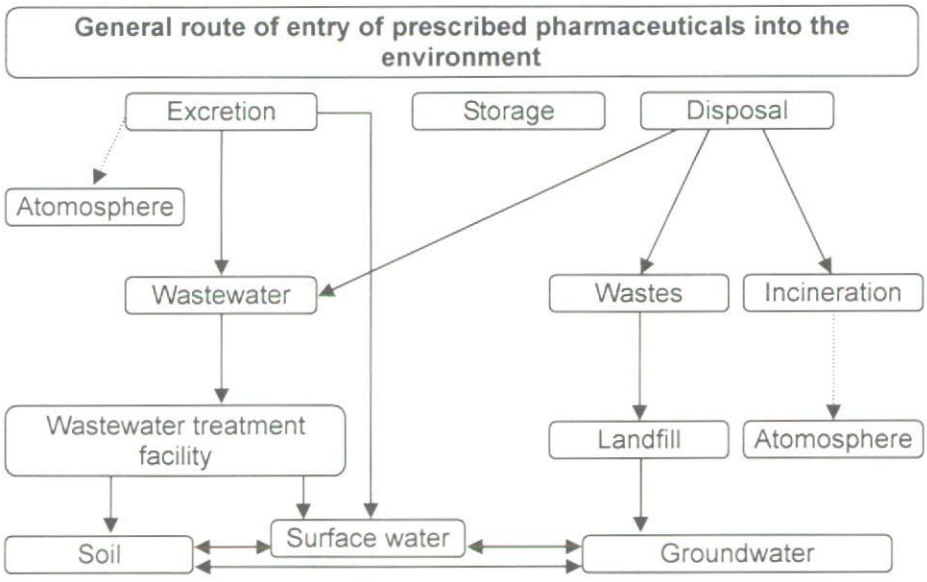


Fig. 3-1-1. The Route of Emission for Pharmaceuticals into the Environment

This emission scenario was used without furtuer modification to derive Eq.1 for estimation of the PEC for surface water. The target pharmaceutical product is assumed to be