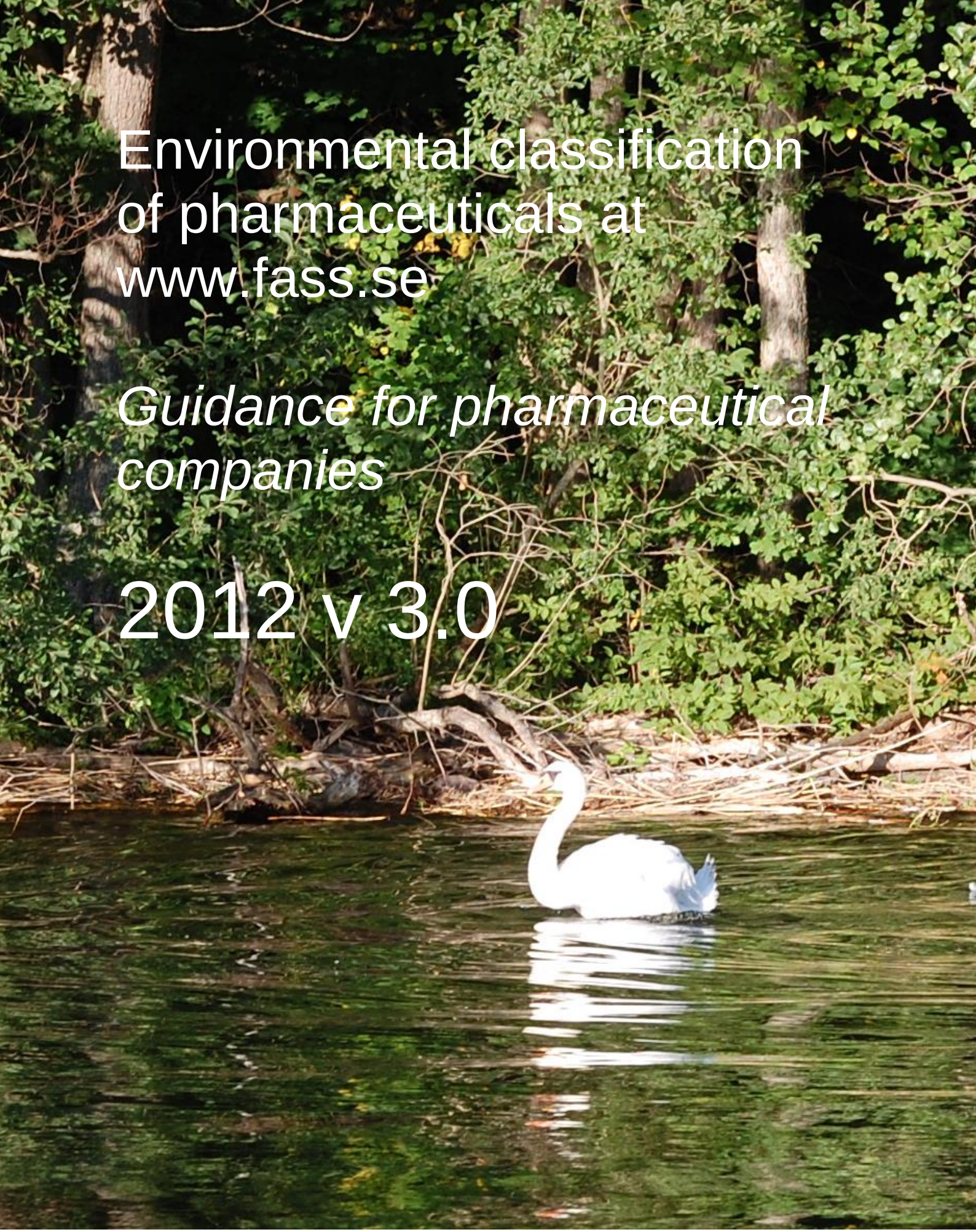
Environmental classification of pharmaceuticals at www.fass.se

Guidance for pharmaceutical companies

2012 v 3.0



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Introduction

The Swedish environmental classification of pharmaceuticals at www.fass.se has now been running since October 2005. Since then a large amount of environmental information of pharmaceuticals has been published.

One of the main reasons for the introduction of environmental information at www.fass.se was the growing public interest in the possible environmental effects of pharmaceuticals. The public interest led to political interest and therefore a significant pressure from the Swedish government for more knowledge about the possible environmental impact of pharmaceuticals.

In 2002, the government instructed the Swedish Medical Products Agency (MPA) to conduct a survey of the state of knowledge on the environmental effects of pharmaceuticals, cosmetics and hygiene products. In its final report, from 2004, the Swedish MPA concluded that EU rules applied and that it was not legally possible to implement a mandatory environmental classification and labelling system in Sweden. Nevertheless, the former Minister of the Environment, Lena Sommestad, made it clear that she expected better information on environmental effects of pharmaceuticals.

Thus Lif, the association for the research based pharmaceutical Industry in Sweden, took the initiative to develop a voluntary environmental classification scheme, in partnership with other interested parties in the healthcare sector. The model was developed in 2004-2005 by Lif, Stockholm County Council, the pharmacy monopoly chain Apoteket AB (today the Swedish Pharmacy Association represents the pharmacies), the Swedish Association of Local Authorities and Regions and the MPA, in conjunction with the international pharmaceutical industry. The goal was to develop a transparent model for the public, the healthcare sector and researchers.

The environmental information, focusing on the aquatic environment, is based on data from the pharmaceutical companies but is reviewed by an independent organization, the Swedish Environmental Research Institute (IVL).

The second time the guideline was updated since the start in 2005 was 2012. The last edition was published in 2007. It is intended that the classification scheme will be reviewed on an on-going basis. Thus, it may be subject to future refinement, based on developing scientific principles, new data and regulatory guidance.

In 2021, a smaller update was made. Primally to update changed conditions such as number of inhabitants in Sweden. The changes made was reviewed by Lif and IVL.

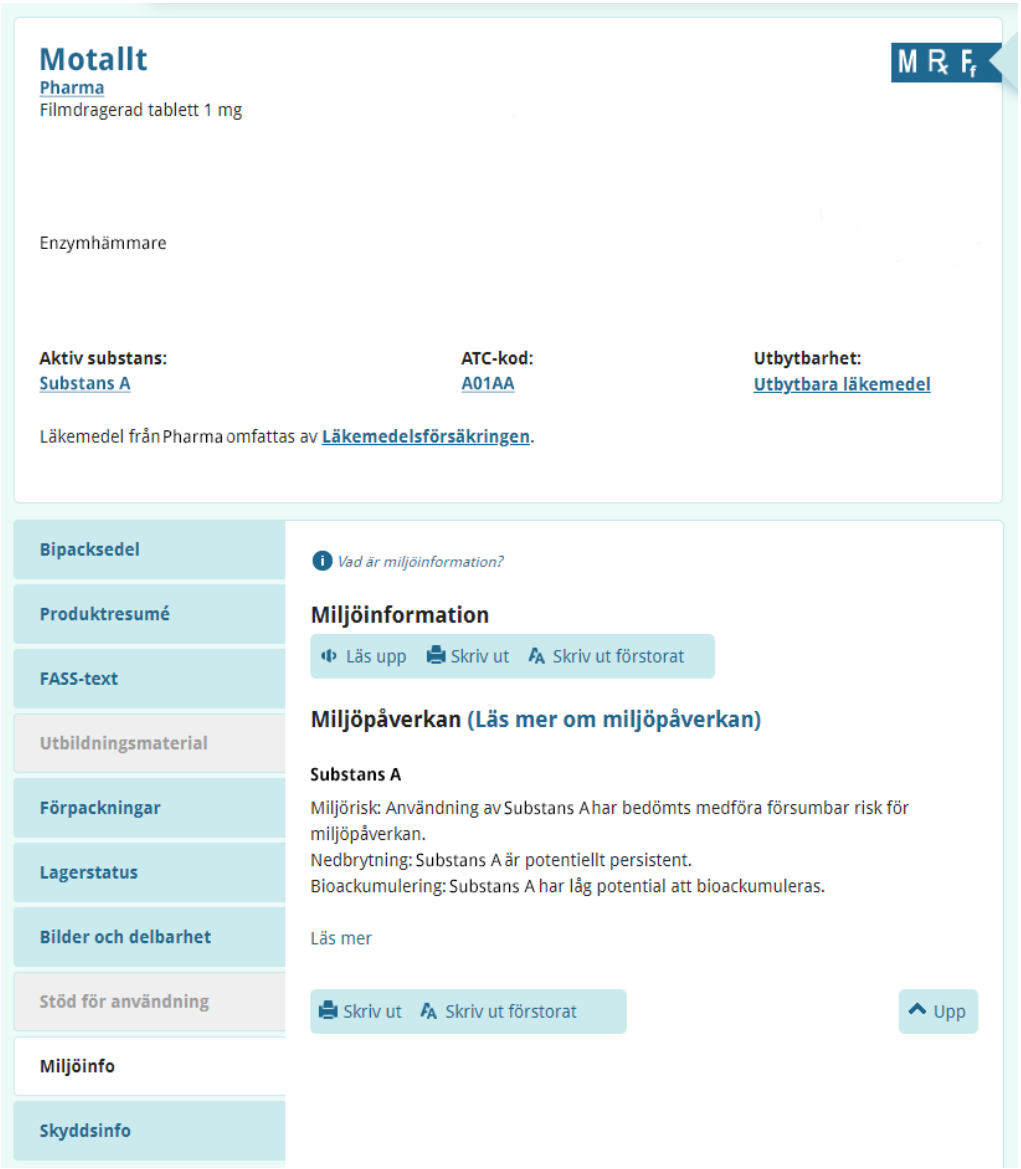
1. Presentation of Environmental Information at www.fass.se

The environmental information is presented at www.fass.se and is available for the Active Pharmaceutical Ingredients (APIs) for each product in the environmental tab called “Miljö” (Figure 1). www.fass.se is the Swedish medicines information portal open to the public.

The first level of information contains summary phrases about the environmental risk, degradation and bioaccumulation. The next level is detailed background information directed to people specifically interested in the environmental data and the underlying basis of the risk assessment.

Please note that the summary phrases will be given in Swedish at www.fass.se, although English translations are available in this document for comparison. However, the detailed background information can be given in English.

Figure 1. The environmental tab “Miljö” at www.fass.se.



1.1 Summary phrases: Environmental risk, degradation and bioaccumulation

The first level of information provides summary phrases based on simple aquatic environmental risk, degradation and bioaccumulation. The environmental risk phrase (Table 1) is based on the PEC/PNEC ratio (Predicted Environmental Concentration / Predicted No Effect Concentration) of the API. The PEC/PNEC ratio decides the wording of the aquatic environmental risk phrase (to be given in Swedish at www.fass.se).

Table 1. Summary phrases for the environmental risk.

Environmental risk		
PEC/PNEC ratio	**Summary phrase, English**	***Summary phrase, Swedish***
PEC/PNEC ≤ 0.1	Use of *name of the substance* has been considered to result in insignificant environmental risk.	*Användning av *substansnamnet* har bedömts medföra försumbar risk för miljöpåverkan.*
0.1 < PEC/PNEC ≤ 1	Use of *name of the substance* has been considered to result in low environmental risk.	*Användning av *substansnamnet* har bedömts medföra låg risk för miljöpåverkan.*
1 < PEC/PNEC ≤ 10	Use of *name of the substance* has been considered to result in moderate environmental risk.	*Användning av *substansnamnet* har bedömts medföra medelhög risk för miljöpåverkan.*
PEC/PNEC > 10	Use of *name of the substance* has been considered to result in high environmental risk.	*Användning av *substansnamnet* har bedömts medföra hög risk för miljöpåverkan.*
If there is no data to calculate the PEC/PNEC.	Risk of environmental impact of *name of the substance* cannot be excluded, since no ecotoxicity data are available.	*Risk för miljöpåverkan av *substansnamnet* kan inte uteslutas då ekotoxikologiska data saknas.*
If there is some, but not sufficient data to calculate the PEC/PNEC.	Risk of environmental impact of *name of the substance* cannot be excluded, since there is not sufficient ecotoxicity data available.	*Risk för miljöpåverkan av *substansnamnet* kan inte uteslutas då det inte finns tillräckliga ekotoxikologiska data.*
If PEC/PNEC <1 but the substance is flagged as a potential PBT (Persistent, Bioaccumulative and Toxic) or vPvB (very Persistent and very Bioaccumulative).	Hazardous environmental properties.	*Särskilt miljöfarliga egenskaper.*

For some APIs, data may be lacking due to limited use/low dose which, in turn, means the action limit in the EU EMA *Environmental Risk Assessment guideline (EMA/CHMP/SWP/4447/00)* of PEC < 0.01 µg/L is not triggered and, consequently, an environmental risk assessment may not have been undertaken. In these cases the following phrase should be included in the detailed background information (to be given in English or Swedish):

*In English: According to the European Medicines Agency guideline on environmental risk assessment of medicinal products (EMA/CHMP/SWP/4447/00), use of * name of the substance* is unlikely to represent a risk for the environment, because the predicted environmental concentration (PEC) at the time of registration was below the action limit 0.01 µg/L.*

*In Swedish: Enligt den europeiska läkemedelsmyndigheten EMA:s riktlinjer för miljöriskbedömning av läkemedelssubstanser (EMA/CHMP/SWP/4447/00), bedömdes det vid registreringstillfället vara osannolikt att användningen av *substansnamnet* kommer att medföra en miljörisk, då det förväntas att användningen ger en koncentration i miljön (PEC) som bli lägre än tröskelvärdet 0,01 µg/L.*

The summary phrases for degradation are given in Table 2.

Table 2. Summary phrases for degradation.

Degradation	
Summary phrase, English	***Summary phrase, Swedish***
Name of the substance is degraded in the environment	**Substansnamnet* bryts ned i miljön.*
Name of the substance is slowly degraded in the environment	**Substansnamnet* bryts ned långsamt i miljön.*
Name of the substance is potentially persistent	**Substansnamnet* är potentiellt persistent.*
The potential for persistence of *name of the substance* cannot be excluded, due to lack of data.	*Det kan inte uteslutas att *substansnamnet* är persistent, då data saknas.*
According to the established EU criteria, *name of the substance* should be regarded as a PBT/vPvB substance.	*I enlighet med EU:s fastställda kriterier ska substansen betraktas som en PBT/vPvB-substans.*

The summary phrases for bioaccumulation are given in Table 3.

Table 3. Summary phrases for bioaccumulation.

Bioaccumulation	
Summary phrase, English	***Summary phrase, Swedish***
Name of the substance has low potential for bioaccumulation.	**Substansnamnet* har låg potential att bioackumuleras.*
Name of the substance has high potential for bioaccumulation.	**Substansnamnet* har hög potential att bioackumuleras.*
The potential for bioaccumulation of *name of the substance* cannot be excluded, due to lack of data.	*Det kan inte uteslutas att *substansnamnet* kan bioackumuleras, då data saknas.*
According to the established EU criteria, *name of the substance* should be regarded as a PBT/vPvB substance.	*I enlighet med EU:s fastställda kriterier ska substansen betraktas som en PBT/vPvB-substans.*

1.1.1 Exempted substances

According to the EU EMA guideline for Environmental Risk Assessment of pharmaceuticals (Ref. 1), vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted because they are unlikely to result in significant risk to the environment. Similarly vaccines and herbal medicinal products are also exempted due to the nature of their constituents.

There might also be other pharmaceuticals on the Swedish market that could be exempted due to the nature of their constituents e.g. activated carbon. In these cases the companies should supply the reviewer with enough information to justify the exemption. Substances that, due to their volatility or other physical parameters, cannot be assessed for aquatic environmental fate and effects are also exempted. The justification of the exemption should be included in the detailed background information.

No environmental information will normally be provided for the exempted pharmaceuticals, and the following summary phrases (Table 4) will be used in the first level of information.

Table 4. Summary phrases for exempted substances

Exempted substances		
Substance	**Summary phrase, English**	***Summary phrase, Swedish***
Vitamins	Use of vitamins has been considered to result in insignificant environmental impact.	*Användning av vitaminer bedöms inte medföra någon miljöpåverkan.*
Electrolytes	Use of electrolytes has been considered to result in insignificant environmental impact.	*Användning av elektrolyter bedöms inte medföra någon miljöpåverkan.*
Amino acids, proteins and peptides	Use of amino acids/peptides/proteins has been considered to result in insignificant environmental impact.	*Användning av aminosyror/peptider/proteiner bedöms inte medföra någon miljöpåverkan.*
Carbohydrates	Use of carbohydrates has been considered to result in insignificant environmental impact.	*Användning av kolhydrater bedöms inte medföra någon miljöpåverkan.*
Lipids	Use of lipids has been considered to result in insignificant environmental impact.	*Användning av lipider bedöms inte medföra någon miljöpåverkan.*
Vaccines	Use of vaccines has been considered to result in insignificant environmental impact.	*Användning av vacciner bedöms inte medföra någon miljöpåverkan.*
Herbal Medicinal Products	Use of herbal medicinal products has been considered to result in insignificant environmental impact.	*Användning av växtbaserade läkemedel bedöms inte medföra någon miljöpåverkan.*
Others	Use of *name of the substance* has been considered to result in insignificant environmental impact.	*Användning av *substansnamnet* bedöms inte medföra någon miljöpåverkan.*

The reviewer may request additional information from companies to justify the exemption and ensure consistency in the approaches used. The justification for an exempted substance should also be given in the detailed background information. If the exemption refers to the EMA guideline (Ref. 1) the detailed background information should also include the following reference phrase (to be given in English or Swedish):

In English: According to the European Medicines Agency guideline on environmental risk assessments for pharmaceuticals (EMA/CHMP/SWP/4447/00), vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates, lipids, vaccines and herbal medicinal products are exempted because they are unlikely to result in significant risk to the environment.

In Swedish: Enligt den europeiska läkemedelsmyndigheten EMA:s riktlinjer för miljörisk-bedömningar av läkemedelssubstanser (EMA/CHMP/SWP/4447/00), är vitaminer, elektrolyter, aminosyror, peptider, proteiner, kolhydrater, lipider, vacciner och växtbaserade läkemedel undantagna då de inte bedöms medföra någon betydande risk för miljön.

Biologically active substances are likely to express similar pharmacological response in biota as their mode of action in humans. Considering that, the justification of the exemption assessed as being biologically active should be amended with the following supplementary phrase (to be given in English or in Swedish):

In English: Even though biomolecules are exempted from environmental risk classification it should be remembered that these molecules may be biologically active.

In Swedish: Även om biomolekyler är undantagna från miljöriskklassificering bör det beaktas att dessa molekyler kan vara biologiskt aktiva.

Depending on the characteristics of the substance, the reviewer may request full environmental information from companies even though the substance is exempted according to the EMA guideline (Ref. 1), e.g. peptides used as antibiotics.

1.2 Detailed background information

Detailed environmental information and the underlying basis of the risk assessment can be found under the link "*Läs Mer"* ('Read More'). Please see section 2.1 Data Collection for guidance on which information to include, and Appendix 1 for an example of how to present data.

Please note that in some cases the detailed background information should include a justification of an exempted substance (see 1.1.1) or a clarification of why environmental data is lacking (see 1.1).

1.3 Data sharing

A mechanism for data sharing, review and publication within the Fass database is available e.g. for generic compounds (i.e. if a company has taken the lead responsibility for compiling the environmental data and undertaking the classification).

Companies lacking environmental data for the APIs will be able to link to the environmental information produced by another company. In that case the following text will automatically appear below the headline "Environmental impact/Miljöpåverkan" (Table 5):

Table 5. Information presented in case of data sharing.

English phrase for data sharing	***Swedish phrase for data sharing***
Environmental information for *name of the substance* originates from *name of the company* for *product name*.	*Miljöinformation för *substansnamnet* är framtagen av *företagsnamnet* för *produktnamnet*.*

1.4 References

References, internal (e.g. company technical reports) or external (publicly available reports and publications), should be given in association with all the submitted data and in a reference list in the end of the detailed background information. Preferably references to original data should be presented and references to Safety Data Sheets should be avoided. The reference should include year of publication and if adequate a version number. On request by the reviewer, additional information should be provided to clarify the data. Confidentiality will be maintained where appropriate.

2. How to assess environmental risk, degradation and bioaccumulation

The following sections describes how to collect data. See Appendix 1 for an example of how to present data.

2.1 Data Collection

It is advisable that the main excreted active form is assessed. If these data are not available, data for the parent compound should be used. For combination products, each active ingredient should be assessed.

It is preferred to use experimental data rather than estimated data (e.g. measured ecotoxicity/D_{ow} vs QSAR). If estimated data are used, the company should justify the scientific rationale.

Environmental information on pharmaceutical compounds published in scientific peer reviewed journals has become more available during the last few years. To make sure all relevant data are considered, companies should take into account relevant published data when evaluating the environmental risk and hazard of the API. The environmental test results, together with the test guidelines followed (OECD, FDA etc.), should be presented. If the test is not standardized, see 2.2.4, 2.3.4, 2.4.1 and Appendix 2 for further guidance.

In some cases the reviewer may request additional information from companies to ensure consistency in the approaches used.

2.1.1 The following information, where available, should be used when classifying the APIs

- Sales data in kilograms of API in Sweden (including all products and enantiomers containing the same API and all salts of the API (e.g. metoprolol succinate and metoprolol tartrate) should be taken into account). If the salt-part (the counter-ion) is subtracted from the total amount this should be explained in the document. For marketed products, data from the most recent year will be provided by Lif in Sweden through cooperation with IQVIA. For newly introduced products (on patent), it is recommended to use the forecasted sales five years after launch when calculating the environmental risk. If forecasted sales data are considered to be confidential, it is allowed to calculate a theoretical interval of quantity substance, based on the environmental risk class to be used, and thereafter state that the forecasted sales in kg are between the limits of this interval.
- Excretion of parent compound after use, as % of given dose.
- Excretion of metabolites after use, as % of given dose, including:

    - Identification of the metabolites, including specification of conjugates, which may deconjugate to the parent compound in a sewage treatment plant.
    - Pharmacological activity (or ecotoxicity, if known) of the metabolites compared with the parent compound.

- Short-term and long-term effects data for algae, crustaceans (usually *Daphnia magna* or *Ceriodaphnia dubia*) and fish. Please provide detailed information about tests eg. test guideline, type of test (eg. acute toxicity or chronic toxicity), test duration, endpoint and species names both in Swedish (or English) and in Latin. Note that growth rate (not

yield/biomass) should be used as endpoint in the Algae growth inhibition test OECD 201 according to ECHA 2017, Guideline R7b, page 28.

- Risk assessment, i.e. PEC/PNEC, calculations as well as the specific PEC and PNEC calculation, given in µg/L, where applicable
- Biodegradation: Ready biodegradability and/or other relevant biodegradation studies where the biomass has not been deliberately pre-exposed to the parent compound (see EMA Q&A, Q 8, p. 5 (Ref. 2)).
- Abiotic degradation: photolysis, hydrolysis, volatilization
- Identification of primary transformation products >10%, where applicable
- Adsorption to sewage sludge (K_{oc}, Kd_{sludge})
- Monitoring data showing sewage treatment plant (STP) removal and/or concentrations in the environment. If any of these data are used, the company should justify the scientific rationale. In some cases the reviewer may request additional information from companies to ensure consistency in the approaches used.
- The bioconcentration factor (BCF), and/or partition coefficient log K_{ow} (often referred to as log P_{ow} or log P). Log D_{ow} or log D_{lipw} can also be used if appropriate.

All data should, where possible, be supported by the appropriate OECD, FDA or similar guidelines. Table 6 shows some comparable test guidelines.

Table 6. Some comparable OECD and FDA test guidelines.

Test	**OECD guideline**	**FDA guideline**
Algal growth inhibition	201	4.01
D. magna, acute toxicity	202	4.08
D. magna, chronic toxicity	211	4.09
Fish, acute toxicity	203	4.11
Hydrolysis	111	3.09
Soil sorption/desorption	106	3.08
Ready biodegradability	301	3.11
Inherent biodegradability	302	3.12

2.2 Environmental Risk Assessment (ERA)

In order to assess the environmental risk of an API, the Predicted Environmental Concentration (PEC) and the Predicted No Effect Concentration (PNEC) need to be calculated.

2.2.1 Predicted Environmental Concentration (PEC)

The PEC is obtained by using the following formula, and is based on the total sales of API in kg/year in Sweden:

Equation

$$PEC\ (\mu g/L) = \frac{A \times 1000000000 \times (100-R)}{365 \times P \times V \times D \times 100} = 1.37 \times 10^{-6} \times A \times (100-R)$$

where:

A (kg/year) = total actual API sales (active moiety) in Sweden for the most recent year (will be obtained from Lif).

R (%) = removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation) = 0 if no data is available.

P = number of inhabitants in Sweden = 10×10^6

V (L/day) = volume of wastewater per capita and day = 200 (ECHA default (Ref. 3))

D = factor for dilution of waste water by surface water flow = 10 (ECHA default (Ref. 3))

The factor of 1000000000 in the equation converts the quantity used from Kg to µg.

The factor of 365 in the denominator converts from annual to daily quantity used. Simplifying all the default values into a single factor gives the second equation.

2.2.1.1 Metabolism

The PEC calculation can consider the extent of metabolism of the active moiety to less pharmacologically active or inactive compounds, e.g. kg x 10% x 0.5 for a metabolite found at a level of 10% and that has half the pharmacological activity of the main active ingredient. This is effectively the same as the FDA approach (Ref. 4). Note, if human metabolism and pharmacological activity of the metabolites are used to refine the PEC calculation, then sufficient data should be provided to support the assumptions made. Specifically, both the amount of metabolite present (as a fraction of excreted material) and the relative pharmacological activity compared to the main active moiety should be provided. It should not be assumed that human metabolites are inactive without supporting information.

If there is uncertainty about the relative potency of metabolites, or the amounts excreted, it is recommended to assume that 100% is excreted as the active parent molecule. This is considered to represent a reasonable worst case.

2.2.1.2 STP removal

STP simulation studies (e.g. OECD 303) can be used directly for predicting removal during sewage treatment. If Ready or Inherent biodegradability test results are available (OECD 301 and 302 series), the SimpleTreat model may be used to calculate removal during sewage treatment (see ECHA Ref. 3, Appendix R.16-3). It is recommended to use SimpleTreat, but alternative models may be used if reasonably justified.

If an OECD 308 study is available and demonstrates >60% mineralization (or 90% primary degradation) by the end of the 100d test period, it is considered reasonable to assume that the substance would be readily removed in a sewage treatment plant. When using SimpleTreat to calculate the removal rate when these criteria are met, the substance may be regarded as “readily biodegradable but failing the 10d window”.

2.2.1.3 Measured Environmental Concentration (MEC)

In principle it should be possible to use measured concentrations (MEC) instead of predicted environmental concentrations, if such data are sufficient to ensure a representative exposure assessment. Adequate supporting information should be provided to justify the interpretation of the results. In some cases the reviewer may request additional information from companies to ensure consistency in the approaches used. In the detailed background information, however, it is still expected to find both the MEC and PEC figures to enable comparison.

2.2.2 Predicted No Effect Concentration (PNEC)

Ideally, ecotoxicological data should be provided for three trophic levels (usually algae, crustaceans (*D. magna* or *C. dubia*) and fish. However, if relevant data are available for the species believed to be most sensitive, based on an understanding of receptor-mediated effects for example, then it may still be possible to derive a PNEC with data from only one or two species.

If a valid PNEC cannot be calculated, the phrases; *'Risk of environmental impact of *name of the substance* cannot be excluded, since no ecotoxicity data are available'* or *'Risk of environmental impact of *name of the substance* cannot be excluded, since there is not sufficient ecotoxicity data available'* should be used.

2.2.2.1 Assessment Factors

The PNEC should preferably be obtained by applying assessment factors (AF) to long-term ecotoxicity data in accordance with the ECHA guidance (Ref. 3, Table R.10-4). If long-term data is lacking, short-term ecotoxicity data may be used. An AF of 1000 is normally applied to the most sensitive of three short-term toxicity tests (LC/EC_{50}) if results from three trophic levels are available. However, the AF may be reduced to 100, 50 or 10, depending on the number of long-term EC_{10} or NOEC endpoints available, providing long-term data are available for the species with the lowest acute LC/EC_{50}.

The AF recommended in the ECHA guidance may not always be applicable, e.g. if particularly sensitive species are identified, based on evaluation of the mode of action of the API, or if mammalian toxicology or data from similar compounds indicate that a higher or a lower AF would be more appropriate. This needs to be considered on a case-by-case basis, with justification provided for the AF used. For instance, cyanobacteria (*Cyanophyta*) are recommended for effects testing of antimicrobials (see EMA guideline, p. 6 (Ref. 1) and EMA Q&A Question 11.1 (Ref. 2)). To calculate the PNEC from an anti-microbial effect study with cyanobacteria, a default AF of 10 is applied to the EC_{10} or NOEC (see EMA guideline, p. 7 (Ref. 1)).

2.2.3 PEC/PNEC ratio

The environmental risk is estimated by calculating the PEC/PNEC ratio. This defines the appropriate risk phrase to be used in the classification scheme. Please see section 1.1.

2.2.4 Use of non-standard data in the ERA

If the test is not standardized, this should be noted, and the company should provide enough information to facilitate interpretation of the results by an independent reviewer and other interested parties. This includes type of endpoint and its ecological relevance, but also other relevant information such as medium, temperature, exposure regime, number of replicates and test geometry (see Appendix 2 for further information).

2.3 Assessment of degradation

This section is intended to assess the degradation potential of the APIs. Note that the phrases do not necessarily relate to the 'P' criteria in PBT/vPvB assessment according to REACH.

Persistence is characterized by the potential for a substance to remain undegraded or unchanged in the environment. Degradation mechanisms can be biotic (biodegradation) and/or abiotic.

In practice, biodegradation in the environment is normally extrapolated from laboratory experiments such as Ready tests (e.g. OECD 301 series), Inherent tests (OECD 302 series) or simulation studies (OECD 303/307/308/309). Mineralisation reduces a pharmaceutical to its basic constituents, which are considered to present no significant environmental risk. Primary degradation of a molecule might also significantly reduce or eliminate its pharmacological activity. In such cases, information should be provided to demonstrate the expected reduction in ecotoxicity. This might be based on direct measurement or, if the identity of the transformation product is known and a suitable analytical standard exists, on a comparison with human metabolites and their relative pharmacological activity, for example.

2.3.1 Interpretation of biodegradation studies (ready and inherent)

If a substance passes the criteria for 'ready' biodegradability, as defined in the OECD 301 test guideline series (or equivalent), the phrase *'The medicine is degraded in the environment'* should be used. If a substance does not pass the criteria for ready biodegradability but the test shows significant mineralisation, the phrase *'The medicine is slowly degraded in the environment'* should be used.

If a substance passes the criteria for 'inherent' biodegradability, as defined in the ECHA Guidance (see below (Ref ECHA Table R. 11-2)), the phrase *'The medicine is slowly degraded in the environment'* should be used:

- Zahn-Wellens test (OECD 302B): pass level - 70% degradation in 7 days, lag-phase no longer than 3 days, percent removal in the test before degradation occurs < 15%, not tested with pre-adapted organisms
- MITI II test (OECD 302C): pass level - 70% degradation should be reached within 14 days, not tested with pre-adapted organisms

If a substance fails to meet the above criteria, and there are no simulation studies or analytical monitoring data to support elimination within the ECHA persistence half-lives, the phrase *'The medicine is potentially persistent'* should be used.

2.3.2 Interpretation of simulation study OECD 308

Fundamentally, the data generated from an OECD 308 study does not lend itself to the generation of independent half-lives for water and sediment since the test system represents a dynamic interaction between the two compartments. Furthermore, the presence of bound (unextractable) sediment residues often makes determination of half-lives in sediment impossible in practice. Consequently, the concept of a 'total system' half-life has been introduced to support this classification scheme.

The following guidance on the interpretation of OECD 308 data represents a practical approach. OECD guidelines do not provide any definitive fail/pass criteria for the OECD 308 study and there is only limited regulatory precedent for the values used in this scheme. This

approach will be reviewed on an on-going basis and may be subject to future refinement based on developing scientific principles, new data and regulatory guidance. The criteria for OECD 308 results for the different degradation phrases are shown in Table 7.

Table 7. Summary of pass criteria for degradation phrases based on OECD 308.

Pass criteria	**Summary phrase**
DT50 ≤ 32d for the total system.	The substance is degraded in the environment.
DT50 ≤ 120d for the total system.	The substance is slowly degraded in the environment.
DT50>120d for the total system.	The substance is potentially persistent.

When assigning a classification based on OECD 308 data, the following points should also be noted:

1. For purposes of this guidance document, DT50 is calculated as the time in days it takes for the amount of total parent material that can be extracted from the whole water/sediment system to reach 50 percent of the initial amount of parent material used to dose the test system. DT50 collectively represents the loss of parent from the test system due to its biological or chemical transformation, mineralization and/or irreversible binding to sediments.

2. For classification purposes, DT50 values should represent the disappearance rate of the parent molecule.

3. The total system DT50 should be calculated from the total amount of parent compound (i.e. water and sediment extractions added together) compared to the total amount applied at the start of the study. In practice, this normally means comparing the amount of radioactivity present as parent compound compared to the total amount of radioactivity applied at the start of the study.

4. The phrase '*The substance is degraded in the environment*' should not be used if there is >15% remaining as parent compound at the end of the study, regardless of the DT50 values obtained. If the DT50 values fulfil the criteria for the phrase '*The substance is degraded in the environment'* but there is in total >15% parent compound remaining at the end of the study (water + sediment extract) then the phrase '*The substance is slowly degraded in the environment'* should be used.

5. As long as all reasonable efforts have been made to extract sediment residues (e.g. by using a range of extraction conditions), any remaining bound residue can be considered as not bioavailable and removed from the system for the purposes of calculating DT50's. Companies should provide brief information on the extraction methods used in order to justify this approach.

6. Normally data for two sediments are available. If, according to the above DT50 criteria, different degradation phrases would be obtained from each sediment, then the phrase '*The substance is slowly degraded in the environment'* should be used. This may occur if the compound is 'degraded' in one sediment and 'slowly degraded' in the other, or if the compound is 'degraded' or 'slowly degraded' in one sediment, but 'potentially persistent' in the other.

7. The cut-off value DT50 ≤ 32d for disappearance of parent extracted from the total system is based on a combination of:

a) The following text from ECHA guidance:

”Rapid degradation in the aquatic environment may be demonstrated by other data than referred to using the standard assessment methods covered above. This may be data on biotic and/or abiotic degradation. Data on primary degradation can only be used where it is demonstrated that the degradation products shall not be classified as hazardous to the aquatic environment, i.e. that they do not fulfil the classification criteria. Scientific evidence must be provided that the substance is degraded in the aquatic environment to a level of >70% within a 28-day period. If first-order kinetics is assumed, which is reasonable at the low substance concentrations prevailing in most aquatic environments, the degradation rate will be relatively constant for the 28-day period. Thus, the degradation requirement will be fulfilled with an average degradation rate constant, $k > 0.043\ day^{-1}$ which corresponds to a degradation half-life of 16 days.”

b) The ratio of 3 for the P criteria for water and sediment (Table 9), and;

c) Taking the mean of the water and sediment half-life to produce a total system half-life.

Thus, in the same way that is 3 x 40d =120d (Table 9), 3 x 16d = 48d. The total system half-life of 32d is then simply the average of 16d and 48d.

8. The cut-off DT50 value of 120d for disappearance of parent extracted from the total system is consistent with the typical duration of an OECD 308 study.

2.3.3 Interpretation of abiotic degradation studies

Abiotic degradation is normally determined from hydrolysis studies (OECD 111) or photodegradation studies (e.g. OECD 316). In principle, these can be used to demonstrate lack of persistence if the predicted half-life in the environment is less than the half-life required to fulfil the ‘P’ criteria (Table 9). However, as discussed above, these are primary degradation mechanisms and hence information on the identity of major transformation products, and their expected ecotoxicity, should also be provided. If these conditions are met the phrase *‘The substance is slowly degraded in the environment’* should be used. If photolysis data are used, consideration should be given to the extrapolation from laboratory to Swedish environmental conditions. For substances that undergo rapid hydrolysis (half-life <40 days at environmentally relevant pH and temperatures) there should be no further biodegradation testing requirements based on the parent compound. Additional fate and effects data should be provided on the hydrolysis products where available.

For substances potentially fulfilling the EU PBT/ vPvB criteria, further information on persistence will be required which may involve a more detailed assessment of the potential ecotoxicity of any significant primary degradation products.

Ultimately, it is the half-life in the environment that is required in order to characterize the persistence of a compound. Hence a ‘weight-of-evidence’ approach is invariably needed in

order to ensure appropriate interpretation of measured and predicted degradation data, particularly where conflicting data exist. In all cases, sufficient supporting evidence should be provided in the detailed background information in order to justify the classification given.

2.3.4 Use of non-standard data when assessing degradation

To ensure consistency within the classification scheme, use of non-standard studies for characterizing persistence should be supported by sufficient information to allow adequate interpretation of the results. Such information could include source and concentration of inoculum; information on pre-exposure, temperature, test substance concentration, DO (dissolved oxygen), pH, analyte (e.g. parent compound or CO_2), number of time points, number of replicates & test geometry.

2.4 Assessment of Bioaccumulation

The most widely accepted measure of bioaccumulation potential is the Bioconcentration Factor (BCF). In order to classify the APIs based on their potential to bioaccumulate, the EU Classification, Labelling and Packaging (CLP) guideline (Ref. 5) is used. According to CLP, a BCF in fish of $\geq$ 500 is indicative of the potential to bioconcentrate, for classification purposes. In the context of PBT/vPvB assessment in the ECHA guidance, the B and vB triggers are BCF=2000 and 5000 respectively (Ref. 3, Table R. 11-1). Note that the phrases do not necessarily relate to the 'B' criteria in PBT/vPvB assessment according to ECHA.

In the absence of a measured BCF value, the bioaccumulation potential may be indicated from log K_{ow} (often referred to as log P_{ow} or log P), which describes partitioning of the neutral form of the molecule. The CLP guideline states that a log K_{ow} > 4 indicates that the substance may bioaccumulate. For complex ionic molecules it is more relevant to use log D_{ow} at pH 7 (see below) (Ref. 3, R.7a, p. 106), but the principle is the same. Note that whilst log D_{ow} ≥4 indicates a potential to bioaccumulate in aquatic organisms, this does not fulfil the 'B' criteria in PBT/vPvB assessment, which would normally be based on a BCF derived from a bioaccumulation study.

Hence, one of the following phrases should be included (Table 8):

Table 8. Bioaccumulation phrases based on test results.

BCF or partition coefficient result	**English phrase**	**Swedish phrase**
BCF < 500 or log D_{ow} (at pH 7) < 4	The substance has low potential for bioaccumulation.	**Substansnamnet* har låg potential att bioackumuleras.*
BCF $\geq$ 500 or log D_{ow} (at pH 7) ≥ 4	The substance has high potential for bioaccumulation.	**Substansnamnet* har hög potential att bioackumuleras.*

The K_{ow} is defined as the partition coefficient of the neutral form of a substance. The D_{ow} is the octanol/water distribution coefficient of all the forms (neutral and ionisable) of a substance and is the actual experimental result. For neutral molecules, D_{ow} will approximate to K_{ow}, but for ionisable molecules K_{ow} is derived by correcting by the acid dissociation constant pK_a using the relationship $K_{ow}=D_{ow}(1+10(abs(pH-pK_a)))$ (Equation 1). However, log K_{ow} and log D_{ow} may both be poor predictors of bioaccumulation for large complex ionisable compounds, as the partitioning mechanism may be more complex than simple partitioning of the neutral species. Hence, use of log D_{ow} (at pH 7) is preferred for ionisable compounds, consistent with ECHA guidance (Ref. 6, R. 7a), as it may better represent the actual

partitioning behaviour, i.e. if log D_{ow} ≥4 at pH 7 then the summary phrase will be *'The substance has high potential for bioaccumulation'*. Care should be taken when using computer-estimated log K_{ow} (ClogP) values, as many of these are based solely on the neutral molecule. If only such values are available, estimated log D_{ow} can be generated from estimated log K_{ow} using Equation 1 above.

Where available, measured liposome/water distribution coefficients (log D_{lipw}) at pH ~7 can be used as a further substitute for bioaccumulation (Ref. 6).

Overall, it should be noted that the use of log K_{ow} relationships, or even log D_{ow}, for estimating BCFs for ionisable compounds is questionable. For example, Meylan *et al.* (Ref. 7) evaluated a large data set of both non-ionic and ionic compounds. Whilst reasonable regression equations were obtained for non-ionic compounds, no acceptable regression was obtained for ionic compounds. These data suggest that significant bioaccumulation potential is unlikely for ionisable compounds. However, the fact that no clear correlations were observed suggests that log K_{ow} may be a poor predictor of bioaccumulation potential.

In summary, for the purpose of this classification scheme, the BCF should be used to select the appropriate phrase. If no measured BCF is available, log $K_{ow,}$ log D_{ow} or log D_{lipw} at pH 7 can be used. However, further discussion concerning the relevance of the available data, possibly referencing the work by Meylan *et al.* (Ref. 7), may be included in the detailed background information.

2.4.1 Use of non-standard data when assessing bioaccumulation

To ensure consistency within the classification scheme, use of non-standard studies for characterizing bioaccumulation should be supported by sufficient information to allow adequate interpretation of the results.

2.5 PBT/vPvB Assessment criteria

The REACH criteria for PBT/vPvB Classification are given in Table 9. For the purpose of this classification scheme, a compound meeting all the criteria given in Table 9 for 'P', 'B' and 'T' ('T' is applicable for PBT, not for vPvB) should be classified as a PBT or vPvB. If the compound is not classified as PBT or vPvB, section 2.5 is not applicable.

Note that the criteria for PBT/vPvB classification in Table 9 to some extent differ from the criteria otherwise specified in this guideline to assess environmental risk, degradation and bioaccumulation.

Table 9. PBT and vPvB criteria according to ECHA

	PBT criteria	**vPvB criteria**
P	Half-life >60 d in marine water or >40 d in freshwater* or half-life >180 d in marine sediment or >120 d in freshwater sediment*.	Half-life >60 d in marine water or freshwater or half-life >180 d in marine or freshwater sediment.
B	BCF >2000	BCF > 5000
T	Chronic NOEC <0.01 mg/L or CMR** or endocrine disrupting effects.	Not applicable.

** For the purpose of marine environmental risk assessment, half-life data in freshwater and freshwater sediment can be overruled by data obtained under marine conditions.*

*** Carcinogenic, Mutagenic or Reprotoxic (Ref. 3, R.11)*

With regard to the compounds that have a PEC/PNEC ratio <1, and at the same time are PBTs and/or vPvBs, these would not be labelled as posing an insignificant or low risk, but rather refer to the hazard information in the detailed background information in accordance with Table 10.

Table 10. Risk and hazard phrases for compounds with PBT and/or vPvB properties

PEC/PNEC ≤ 1, fulfilling PBT/vPvB criteria		
Test result	**Summary phrases**	**Detailed background information**
PEC/PNEC ≤ 1, fulfilling PBT criteria	Hazardous environmental properties. According to the established EU criteria, the compound should be regarded as a PBT/vPvB substance. *In Swedish: Särskilt miljöfarliga egenskaper. I enlighet med EU:s fastställda kriterier ska substansen betraktas som en PBT/vPvB-substans.*	The calculated PEC/PNEC ratio is ≤ 1. Hence, risk assessment procedures would indicate that "Compound A" would have insignificant/low* long-term risk to the environment. However, the half-life in the environment** is >xx days, the BCF is >2000 and the chronic toxicity is <0.01 mg/L (NOEC). "Compound A" should therefore be regarded as a PBT substance, according to the ECHA Guidance criteria, and as such the current PEC/PNEC ratio may underestimate the potential for long-term risks to aquatic organisms. *In Swedish: Den beräknade PEC/PNEC-kvoten är ≤ 1. Denna kvot indikerar normalt att "Ämne A" medför försumbar/låg* risk för miljöpåverkan. Dock är halveringstiden i miljön** >xx dagar, BCF är >2000 och den kroniska toxiciteten är <0,01 mg/L (NOEC). "Ämne A ska därför betraktas som en PBT-substans enligt ECHA:s kriterier, och det är därför möjligt att den aktuella PEC/PNEC-kvoten underskattar risken för långtidseffekter på vattenlevande organismer.*
PEC/PNEC ≤ 1, fulfilling vPvB criteria	Hazardous environmental properties. According to the established EU criteria, the compound should be regarded as a PBT/vPvB substance. *In Swedish: Särskilt miljöfarliga egenskaper. I enlighet med EU:s fastställda kriterier ska substansen betraktas som en PBT/vPvB-substans.*	The calculated PEC/PNEC ratio is ≤ 1. Hence, risk assessment procedures would indicate that "Compound A" would have insignificant/low* long-term risk to the environment. However, the half-life in the environment** is >xx days and the BCF is >5000. "Compound A" should therefore be regarded as a vPvB substance, according to the ECHA Guidance criteria, and as such the current PEC/PNEC ratio may underestimate the potential for long-term risks to aquatic organisms. *In Swedish: Den beräknade PEC/PNEC-kvoten är ≤ 1. Denna kvot indikerar normalt att "Ämne A" medför försumbar/låg* risk för miljöpåverkan. Dock är halveringstiden i miljön** >xx dagar och BCF är >5000. "Ämne A" ska därför betraktas som en vPvB-substans enligt ECHA:s kriterier för vPvB-klassificering, och det är därför möjligt att den aktuella PEC/PNEC-kvoten underskattar risken för långtidseffekter på vattenlevande organismer.*
PEC/PNEC > 1, fulfilling PBT/vPvB criteria		

Test result	Summary phrases	Detailed background information
PEC/PNEC > 1, fulfilling PBT criteria	Use of the medicine has been considered to result in moderate /high* environmental risk. Hazardous environmental properties. According to the established EU criteria, the compound should be regarded as a PBT/vPvB substance. *In Swedish: Användning av läkemedlet har bedömts medföra medelhög/hög* risk för miljöpåverkan.* *Särskilt miljöfarliga egenskaper.* *I enlighet med EU:s fastställda kriterier ska substansen betraktas som en PBT/vPvB-substans.*	Use of the medicine has been considered to result in moderate/high* environmental risk. In addition, the half-life in the environment** is >xx days, the BCF is >2000 and the chronic toxicity is <0.01 mg/L (NOEC). “Compound A” should therefore be regarded as a PBT substance according to the ECHA Guidance criteria. *In Swedish: Användning av läkemedlet har bedömts medföra medelhög/hög* risk för miljöpåverkan. Dessutom är halveringstiden i miljön** >xx dagar, BCF är >2000 och den kroniska toxiciteten är <0,01 mg/L (NOEC). ”Ämne A” ska därför betraktas som en PBT-substans enligt ECHA:s kriterier.*
PEC/PNEC > 1, fulfilling vPvB criteria	Use of the medicine has been considered to result in moderate/high* environmental risk. Hazardous environmental properties. According to the established EU criteria, the compound should be regarded as a PBT/vPvB substance. *In Swedish: Användning av läkemedlet har bedömts medföra*	Use of the medicine has been considered to result in moderate/high* environmental risk. In addition, the half-life in the environment** is >xx days and the BCF is >5000. “Compound A” should therefore be regarded as a vPvB substance according to the ECHA Guidance criteria. *In Swedish: Användning av läkemedlet har bedömts medföra medelhög/hög* risk för miljöpåverkan. Dessutom är halveringstiden i miljön** >xx dagar och BCF är >5000. ”Ämne A” ska därför betraktas som en vPvB-substans enligt EU TGD:s kriterier.*

	medelhög/hög risk för miljöpåverkan.* *Särskilt miljöfarliga egenskaper.* *I enlighet med EU:s fastställda kriterier ska substansen betraktas som en PBT/vPvB-substans.*	

** delete as appropriate*
*** specify environmental compartment (seawater/freshwater/sediment etc)*

3. Quality assurance process

Development of this guideline has been overseen by a multi stakeholder group including representatives from the research-based pharmaceutical industry, Lif, the Stockholm County Council, the Swedish Association of Local Authorities and Regions, the pharmacy monopoly chain Apoteket AB (today the Swedish Pharmacy Association represents the pharmacies), and the Swedish Medical Products Agency.

To ensure consistent application of the guideline, an independent reviewer, IVL, the Swedish Environmental Research Institute, has been appointed to review the information submitted by companies (Figure 2). The reviewer will check the data submitted and that the guideline has been applied correctly, making recommendations for amendments where appropriate. On occasions the reviewer may request further information from the company, via Lif, if required to support the proposed classification phrases. However, it is important to note that individual companies are ultimately responsible for the environmental summaries entered into the Fass database.

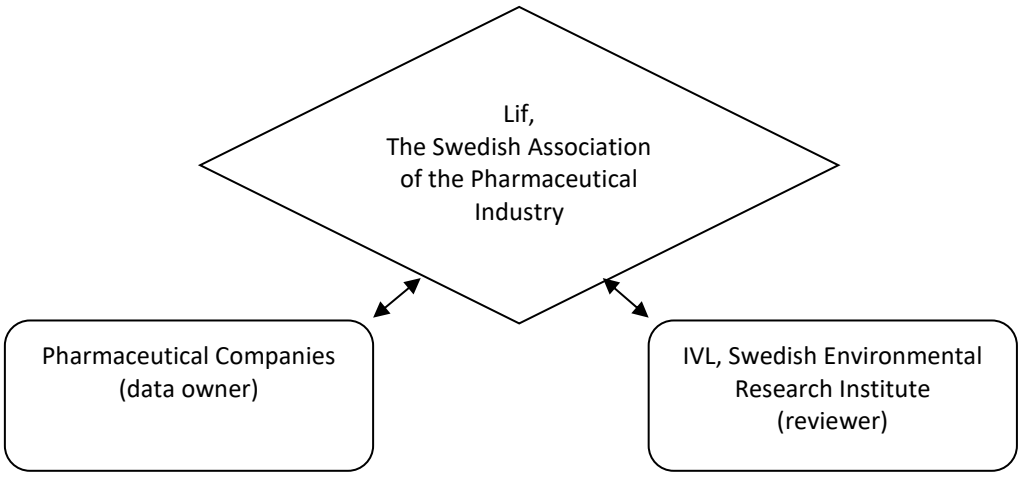


Figure 2. Partners in the quality assurance process of environmental classification at www.fass.se.

4. References

1. Committee for Medicinal Products for Human Use (CHMP); Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use. 1 June 2006, Ref EMEA/CHMP/SWP/4447/00.
2. EMA Q&A for Environmental Risk Assessment http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/04/WC500105107.pdf
3. ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment. http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm
4. Guidance for Industry. Environmental Assessment of Human Drug and Biologics Applications. US Department of Health and Human Services, Food and Drug Administration, July 1998. CMC 6, Revision 1. http://www.fda.gov/cder/guidance/1730fnl.pdf
5. Guidance to regulation (EC) No1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. European Chemical Agency, http://guidance.echa.europa.eu/docs/guidance_document/clp_en.pdf
6. Escher BI, Hermens JLM. 2004. Internal exposure: linking bioavailability to effects. Environ Sci Technol Dec 1, 2004: 455A–462A.
7. Meylan, W.M, Howard, P.H., Boethling, R.S., Aronson, S., Printup, H. and Gouchie, S. 1999. Improved method for estimating bioconcentration/bioaccumulation factor from octanol/water partition coefficient. Environ. Toxicol. Chem. 18, 664-672.

5. Document history

Version	Date	Changed by	Changes
1.0	2012		First version.
2.0	2021	Lif and IVL	General: LIF --> Lif and IMS Health --> IQVIA Introduction – added information regarding the update don in 2021 1 – figure 1 updated. 1.1 – update of the Swedish translation for the phrase given when environmental risk assessment may not have been undertaken. Added information regarding that even though biomolecules are exempted from environmental risk classification it should be remembered that these molecules may be biologically active. 1.4 – added information; Preferably references to original data should be presented and references to Safety Data Sheets should be avoided. The reference should include year of publication and if adequate a version number. 2 – added information; The following sections describes how to collect data. See Appendix 1 for an example of how to present data.

			2.2.1 – added information; If the salt-part (the counter-ion) is subtracted from the total amount this should be explained in the document. Updated information regarding Short-term and long-term effects data for algae, crustaceans and fish. Updated number of inhabitants in Sweden (Also updated in Appendix 1) 2.2.2 – added information regarding that EC_{10}-data can be used for long time studies. (Also updated in Appendix 1) 2.2.2.1 – added information; “if results from three trophic levels are available”. Added information regarding $EC_{10.}$ 2.3.2 5. – clarification that only brief information is needed. 2.3.4 – clarification of the the abbreviation “DO”. 2.5 – updated text regarding REACH/PBT/vPvB Classification. 5 – document history added Appendix 1 – updated text regarding *PNEC (µg/L) = lowest EC_{10} or NOEC/10, where 10is the assessment factor used for three long-term ecotoxicity data endpoints. EC_{10} for rainbow trout has been used for this calculation since it is the most sensitive of the three tested species*
3.0	2021	Lif	Minor update 2.2.1 and Appendix 1 – equation updated so it matches P that was updated in version 2.0.

6. Appendix 1 - Template for environmental information at www.fass.se

Substance X

Environmental risk: Use of *name of the substance* has been considered to result in insignificant environmental risk.
Degradation: *Name of the substance* is slowly degraded in the environment.
Bioaccumulation: *Name of the substance* has low potential for bioaccumulation.

Detailed background information

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

PEC (µg/L) = $(A*10^{9}*(100-R))/(365*P*V*D*100) = 1.37*10^{-6}*A(100-R)$

PEC = xx µg/L

Where:

A = xx kg (total sold amount API in Sweden year 20xx, data from IQVIA). *Reduction of A may be justified based on metabolism data.*

R = X % removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation) = 0 if no data is available. (*If R ≠0 this should be justified under the degradation section*)

P = number of inhabitants in Sweden = $10*10^{6}$

V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (Ref. I)

D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (Ref. I)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies*

Algae (Latin name) (guideline eg OECD 201) (Reference II)*:*

EC_{50} 72 h (endpoint) = xx µg/L

EC_{10} or NOEC = xx µg/L

Crustacean (Latin name):

Acute toxicity

EC_{50} xx h (endpoint) = xx µg/L (guideline eg OECD 202) (Reference)

Chronic toxicity

EC_{10} or NOEC xx days (endpoint) = xx µg/L (guideline eg OECD 211) (Reference)

Fish (Latin name):

Acute toxicity

LC_{50} xx h (endpoint) = xx µg/L (guideline eg OECD 203) (Reference)

Chronic toxicity

EC_{10} or NOEC xx days (endpoint) = xx µg/L (guideline eg OECD 210) (Reference)

Other ecotoxicity data: PNEC = xx µg/L (justification of chosen assessment factor (AF))

e.g.
"PNEC (µg/L) = lowest EC_{10} or NOEC/10, where 10 is the assessment factor used for three long-term ecotoxicity data endpoints. EC_{10} for rainbow trout has been used for this calculation since it is the most sensitive of the three tested species.

**if the ecotoxicological test is not standardised please specify the test with additional relevant data (e.g. medium, temperature, exposure regime, number of replicates & test geometry)*

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = xx/xx = xx, i.e. PEC/PNEC ≤ xx which justifies the phrase 'Use of *name of the substance* has been considered to result in insignificant/low/moderate/high environmental risk.'

Degradation*

Biotic degradation

Ready degradability:

Test results eg % degradation in xx days (guideline eg OECD 301). (Reference)

Inherent degradability:

Test results eg % degradation in xx days (guideline eg OECD 302). (Reference)

Simulation studies:

Test results eg DT50 in water, sediment and total system (guideline eg OECD 308). (Reference)

Abiotic degradation

Hydrolysis:

Test results eg % degradation in xx days (guideline eg OECD 111). (Reference)

Photolysis:

Test results eg % degradation in xx days (guideline eg OECD 316). (Reference)

Justification if R ≠0, eg modelling results using SimpleTreat:

Justification of chosen degradation phrase:

Substance X passes the ready degradation test but is not inherently degradable. The phrase "*Name of the substance* is slowly degraded in the environment" is thus chosen.

**If the degradation test is not standardised please specify the test with the following additional data if available; source & concentration of inoculum, information on pre-exposure, temperature, test substance concentration, DO, pH, analyte (e.g. parent compound or CO2), number of time points, number of replicates & test geometry.*

Bioaccumulation

Bioconcentration factor (BCF):

Test result (guideline eg OECD 305). (Reference)

Partitioning coefficient:

e.g. Log D_{ow} = xx at pH 7 (guideline eg OECD 107). (Reference)

Justification of chosen bioaccumulation phrase:

Since BCF < 500, the substance has low potential for bioaccumulation.

or;

Since log D_{ow} < 4 at pH 7, the substance has low potential for bioaccumulation.

Excretion (metabolism)

Substance X is excreted to xx% as parent compound and to xx% as metabolites. The pharmacological activity of the metabolites is not known. (Reference)

A reduction of A (total sold amount API in Sweden 20xx) *in the PEC calculation based on metabolism should be justified here.*

PBT/vPvB assessment

If Substance X fulfils the criteria for PBT and/or vBvP this should be flagged and the following phrase should be added: According to the established EU criteria, the compound should be regarded as a PBT/vPvB substance.

References

I. ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment. http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm
II. Study report..……

7. Appendix 2 - Examples of criteria for non-standardised tests

Please find some guidance below on endpoints related to ecological significance, to be used for evaluating non-standard tests (from Technical Guidance for Deriving Environmental Quality Standards (EQS) (Ref I)).

"A study can be well conducted and fully reported but the test endpoint may have little ecological significance. Studies used for EQS development should be those where the test endpoint can be related to ecologically significant hazards. For practical purposes, this means effects that can be linked to population sustainability and particularly:

a) survivorship of adults

b) time taken to develop (particularly to reach reproductive age)

c) reproductive output

Most standard test methods include one or more of these endpoints. However, the assessor may be faced with data from studies describing endpoints that do not include direct measurements of survival, development or reproduction e.g. behavioural effects, anatomical differences between control and treatment groups, effects at the tissue or sub-cellular level, such as changes in enzyme induction or gene expression. Generally these are unsuitable as the basis for EQS derivation. However, anatomical changes to gonad development that would prevent successful reproduction, or changes in behaviour if the effect described would impair competitive fitness may be relevant."

For more guidance on criteria that are suitable to evaluate non-standardised tests, please see Küster *et al.* (2009) (Ref. II).

References

I. Technical Guidance for Deriving Environmental Quality Standards (EQS). 2011. Common Implementation Strategy for the Water Framework Directive (2000/60/EC). Guidance Document No. 27. European Commission. Technical Report – 2011 – 055. ISBN: 978-92-79-16228-2.

II. Küster, A., J. Bachmann, J., Brandt, U., Ebert, I., Hickmann, S., Klein-Goedicke, J., Maack, G., Schmitz, S., Thumm, E. and Rechenberg, B. 2009. Regulatory demands on data quality for the environmental risk assessment of pharmaceuticals. Regul. Toxicol. Pharmacol. 55, 276-280.