Swedish Environmental Research Institute

Self-declarations of environmental classification at fass.se

Experiences from the reviewing process 2022

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Summary

This report provides an overview of the review process of environmental classifications of pharmaceuticals at fass.se in 2022. We believe that this review is important for the quality control of the environmental classifications, to ensure the publication of reliable and mutually comparable environmental data.

By summarizing the work done in 2022, this report contributes to the continuous improvement of the environmental classification process on fass.se. Providing accurate and up-to-date environmental information to users, is essential for promoting sustainability and informed decision-making. The environmental information published at fass.se is a valuable resource for e.g. Swedish Drug and Therapeutics Committees, physicians, pharmacists and other stakeholders interested in the environmental impact of pharmaceuticals, facilitating comparisons between pharmaceuticals and contributing to informed decision-making.

In 2022, environmental documents for 356 unique substances were published at fass.se. Of these, 26% were classified regarding environmental risk, 54% were exempted substances, and 20% were not possible to classify due to inadequate data.

The majority of substances assessed during 2022 posed "insignificant environmental risk" (89%). Only 4, out of all substances with environmental classifications published at fass.se, were classified as "hazardous" by the end of 2022.

Approximately 41% of the substances assessed 2022 were possible to assess for bioaccumulative potential, with 92% indicating "low potential to bioaccumulate". A total of 39 substances, with environmental classifications published at fass.se, were classified as posing a "high potential to bioaccumulate".

Of the environmental documents published in 2022, 62% of the substances which were possible to assess for persistence were classified as “potentially persistent". 158 substances in total at fass.se have that classification.

Sammanfattning

Denna rapport ger en översikt över granskningsprocessen av miljöklassificeringen av läkemedel på fass.se år 2022. Granskningen är viktig för kvalitetskontrollen för att säkerställa att de miljödokument som publiceras är korrekta och inbördes jämförbara.

Genom att sammanfatta arbetet som utfördes år 2022 vill vi bidra till den kontinuerliga förbättringen av miljöklassificeringsprocessen på fass.se. Att tillhandahålla korrekt och aktuell miljöinformation till användarna är avgörande för att främja hållbarhet och möjliggöra informerade beslut. Den miljöinformation som publiceras på fass.se utgör en värdefull resurs för exempelvis regionernas läkemedelskommittéer, läkare, apotekare och andra som är intresserade av läkemedlens miljöpåverkan, vilket underlättar jämförelser mellan olika läkemedel och bidrar till välgrundat beslutsfattande.

Under 2022 publicerades miljödokument för 356 unika substanser på fass.se. Av dessa klassificerades 26% gällande miljörisk, 54% var undantagna ämnen, och 20% var inte möjliga att klassificera på grund av otillräckliga data.

Majoriteten (89%) av ämnena som bedömdes under 2022 fick klassificeringen "försumbar risk för miljöpåverkan". Endast 4 ämnen sammanlagt, av alla ämnen som har miljödokument publicerade på fass.se, klassificerades vid årsslutet 2022 som att de har "särskilt miljöfarliga egenskaper". Ungefär 41% av de ämnen som bedömdes år 2022 gick att bedöma avseende bioackumuleringspotential, varav 92% indikerade "låg potential att bioackumuleras". Sammanlagt totalt 39 ämnen med miljödokument på fass.se klassificerades "hög potential att bioackumuleras".

Av de miljödokument som publicerades år 2022 klassificerades 62% av ämnena, som var möjliga att bedöma när det gäller nedbrytning, som "potentiellt persistenta". Totalt har 158 ämnen på fass.se den klassificeringen.

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1 Introduction

In Sweden, both healthcare professionals and the public can access information on pharmaceuticals on the web portal www.fass.se. Since 2005 this portal has also included environmental information about the substances, according to a classification system for pharmaceutical substances developed on the initiative by Lif, the association for the research based pharmaceutical industry in Sweden. 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. The classification system is based on self-declaration, where each pharmaceutical company is responsible for their own environmental information. Prior to publication the environmental risk assessments are reviewed by IVL Swedish Environmental Research Institute (IVL) as an independent, external part.

1.1 Aim

The overall aim of the FASS-project during 2022 was to keep a good quality of the environmental documents presented at fass.se and to continue to develop and strengthen the Swedish environmental classification system to make it a powerful tool on a national level, as well as to raise acceptance and interest on an international level. This included continued review of the companies' interpretation of the guidance and in-depth discussions with Lif in cases where additional guidance was needed beyond what is found in the FASS guidance.

1.2 Background

Pharmaceutical products are essential for health and well-being in our everyday life. Benefits of the use of pharmaceuticals may come with an environmental downside, though. Pharmaceutical residues in the environment have thus become a prioritized area within environmental surveillance as well as within environmental risk assessment.

In 2005 environmental information was first published at fass.se to test a new model for classification, developed on the initiative by Lif. The initiative was a

response to an increasing public demand for environmental information on pharmaceuticals and an attempt to develop a model accepted by both Swedish stakeholders, and by the global pharmaceutical industry. In 2010, environmental risk assessment had been conducted for all groups of pharmaceuticals (ATC codes) on the Swedish market.

The environmental classification at fass.se is a self-declaration system - each pharmaceutical company is responsible for the environmental information published on the portal. Prior to publication the classifications are reviewed by IVL, as an independent external part, to make sure that the classifications are based on a scientifically acceptable interpretation of the guidance by the pharmaceutical companies. The reviewing process ensures a common praxis for the implementation of the guidance (Lif 2021) among the companies and feeds back experience from the self-declaration process to the system owners, Lif. The review process also gives support and help to the companies to conduct the environmental risk assessments according to the principles in the guidance (Lif 2021), thus supporting the quality and credibility of the system. The classifications are, according to the principles of the system, to be updated and reviewed every three years. If a new document is not sent in for review after three years, the information about environmental risk is unpublished from fass.se. In the reviewing process, issues in need for further investigation are continuously coming up. This can be due to availability of new data or knowledge in the field, as well as possibilities of comparisons between different pharmaceuticals with the same active pharmaceutical ingredient. To keep its credibility, it is important that the system is continuously reviewed and improved. The work on the review of the environmental risk assessments at fass.se is conducted in close connection with related research studies, which form the basis for the development of the reviewing process.

1.3 The guidance and the review process

The guidance for which environmental data to use to support and differentiate the classification steps were developed by the Lif-secretariat and the Lif Expert Group on Sustainable Development, including representatives from the industry, the Stockholm County council, the pharmacy chain Apoteket, the Swedish Association of Local Authorities and Regions (SALAR/SKL) and the Swedish Medical Products Agency (MPA). After the deregulation of the pharmacy market in Sweden the pharmacy chain Apoteket has been replaced by the Swedish Pharmacy Association in the dialogue. The first guidance was published in 2007 (Lif 2007) and a revised

document was presented in June 2012. A minor update of the guidance was done in 2021 and the latest version is now 2012 v 3.0.

In addition to the risk phrase for environmental risk, which concerns the risk of ecotoxicological effects, each substance is also assigned hazard phrases for bioaccumulation and persistence. Certain substances can be exempted from classification, in accordance with the European Medicines Agency Guideline (EMA 2006), if they are unlikely to result in significant risk to the environment, e.g. proteins, vitamins and electrolytes.

In the environmental classification of pharmaceuticals at fass.se, the risk posed by the pharmaceuticals is differentiated into five different categories based on its PEC/PNEC-value and if it is a PBT/vPvB-substance (Persistent, Bioaccumulative, and Toxic or very Persistent and very Bioaccumulative):

- insignificant risk
- low risk
- moderate risk
- high risk
- hazardous

The environmental assessment at fass.se is presented at two different levels. For the non-expert user, the summary phrases describe the classifications regarding environmental risk, degradation and bioaccumulation assigned to the substance. For the expert reader a second level includes more information on the basis for the self-declaration, including a list of references.

Before the publication of environmental data at fass.se, the risk and hazard assessments are reviewed by IVL. Based on the supporting data IVL assesses the classifications made by the company and the choice of classification phrase in the three categories environmental risk, bioaccumulation and persistence. If revision is needed, the company is encouraged to send the risk assessment for another review before publication.

The review by IVL can result in comments in four categories:

- **Major deviation** – deficiencies in the submitted material leads to an inaccurate classification of risk and/or hazard and needs to be changed before publication at fass.se

- **Minor deviation** - deficiencies in the submitted material that does not lead to an inaccurate classification of risk and/or hazard but still needs to be changed before publication at fass.se

- **Remark** – minor deficiencies, correction is recommended (although not mandatory) to be in full compliance with the guidance

- **No remarks** – the submitted material follows the guidance and the document is recommended for publication.

2 Experiences from the reviewing process during 2022

The audit team at IVL keeps track of documents that have been reviewed, or are under current review, in a spreadsheet. The data recorded is saved over time and extends back to October 2009. The statistic calculations presented here are based on data for the year 2022.

This report presents data and reasoning about active pharmaceutical ingredients (API). The terms pharmaceuticals and substances are also used, in the report they all refer to API.

2.1 Statistics of the review process

The total number of reviews during 2022 was 494 (a company may send in documents for the same substance several times) and the most common assessment from IVL was to give no remarks (69%). During 2022, 416 environmental risk assessments with unique substance/pharmaceutical company-combinations were submitted for review. The highest grade of comment that each company received for their risk assessments for a specific substance is illustrated in Figure 1. The majority (84%) of the environmental risk assessments got the comments “no remarks” or “remark”. The remaining 16% got a comment that needed to be corrected before publication. In total, risk assessments for 400 different substances (several companies may send in risk assessments for the same substance) were reviewed during 2022.

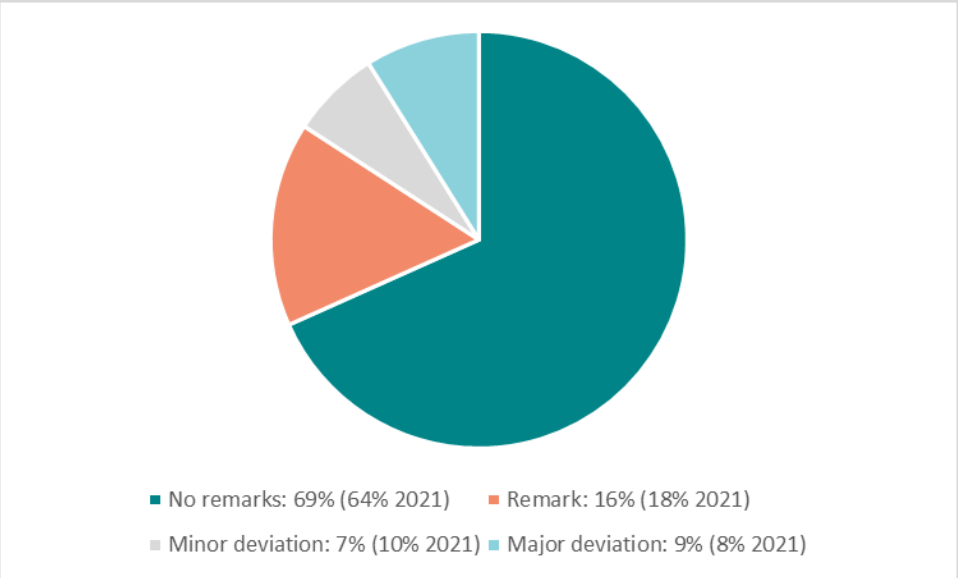

Figure 1. Distribution of the highest grade of recommendations that each company received for a specific substance that was sent in for review during 2022.

3 Results of the classification

The statistics below are based on data from Lif, showing a snapshot of all the risk assessments that are published at fass.se at the time of data collection. The data is retrieved as close as possible to the end of every year, to facilitate comparisons between different years. The statistics include all the environmental risk assessments that had been published during 2022 and that could be viewed at fass.se at 2022-12-22.

In total there are 1165 documents with environmental risk classification of pharmaceuticals published at fass.se. 369 documents were published during 2022 (new or updated documents). This corresponds to 944 unique substances in total at fass.se, and 356 unique substances whose information was published in 2022.

3.1 Environmental classification of substances

The total number of unique substances that was published at fass.se during 2022 was 356, which corresponds to 369 environmental risk assessments. This number differs from the number of assessed substances since a substance assessed at the end of the year might be published on fass.se the year after. The larger number of risk assessments in comparison to the number of unique substances is due to the

fact that one substance can be marketed and, thus, risk assessed by more than one company. 26% of the 356 unique substances were classified regarding environmental risk, 54% were exempted substances and another 20% were reviewed, but no classification could be made (either due to lack of data or insufficient data). The distribution of the unique substances is illustrated in Figure 2.

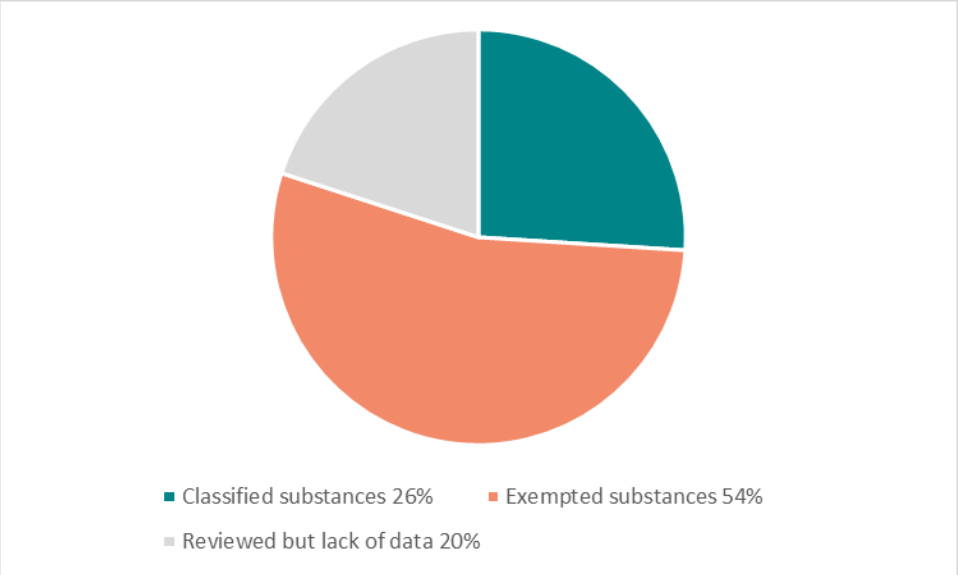

Figure 2. Environmental classification of substances published at Fass.se during 2022 (n = 356). The figure covers classification of environmental risk, i.e., not the classifications for potential for degradation or for bioaccumulation.

3.2 Environmental risk

The environmental risk phrase is based on the PEC/PNEC ratio (Predicted Environmental Concentration/Predicted No Effect Concentration) of the API (Active Pharmaceutical Ingredient). Depending on the PEC/PNEC ratio the substance will be classified in one out of four categories:

- Insignificant risk e.g. PEC/PNEC ≤0.1
- low risk e.g. PEC/PNEC 0,1 - ≤1
- moderate risk e.g. PEC/PNEC >1 - ≤10
- high risk. eg. PEC/PNEC >10

When the PEC/PNEC <1, but the substance is flagged as potential PBT (Persistent, Bioaccumulative, and Toxic) or vPvB (very Persistent and very Bioaccumulative), the substance is classified as having hazardous environmental properties. Of the 92

substances (26%) with enough data to calculate a PNEC-value, and thus classify the environmental risk, 89% were classified as posing an insignificant risk, 8% were classified as low risk, 1% as moderate risk, 2% as high risk and none of the substances was classified as being hazardous (Figure 3).

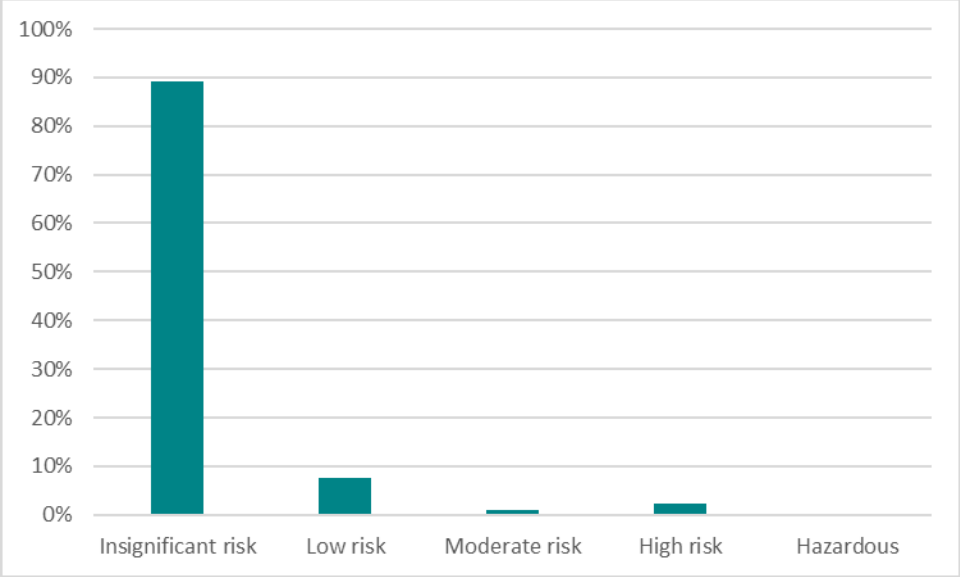

Figure 3. Outcome of the environmental risk assessments of pharmaceuticals at Fass.se, assessed during 2022 (n =92).

Two substances published during 2022 were classified as posing high environmental risk: Abiraterone acetate (a substance that stops the production of testosterone and is used for treatment of prostate cancer) and Finerenone (a substance which block mineralocorticoids (a class of steroid hormones) and is used as a treatment for chronic kidney disease). One substance published during 2022 was classified as posing moderate environmental risk: Estrogens, conjugated (mixture of different female sex hormones, estrogens, used for hormone replacement therapy during e.g. menopause).

At the end of the year 2022 only 4 substances, in total of all substances published at fass.se, were classified as hazardous, 6 substances were classified with high risk and 12 substances were classified with moderate risk.

3.3 Potential to bioaccumulate

Of the 356 unique substances published at fass.se during 2022, 145 (41%) were assessed for bioaccumulative potential. A substance is classified as posing high potential for bioaccumulation if the Bioconcentration factor (BCF) is greater than

500 or Log K_{ow} >4. For 18 substances (5%) data to make an assessment were not available and 193 substances (54%) were exempted, and thus a hazard phrase was not assigned.

As shown in Figure 4, the vast majority (92%) of the substances assessed 2022, with a classification of the bioaccumulative potential, were assigned a hazard phrase indicating a low potential to bioaccumulate. For pharmaceuticals, often designed to be hydrophilic to enhance transportation in the body, this is to be expected. Many substances also undergo metabolism to more hydrophilic forms in the human body.

At the end of 2022, 39 substances classified as posing a high potential to bioaccumulate were published in total on fass.se. Out of them 11 substances were assessed and published during 2022.

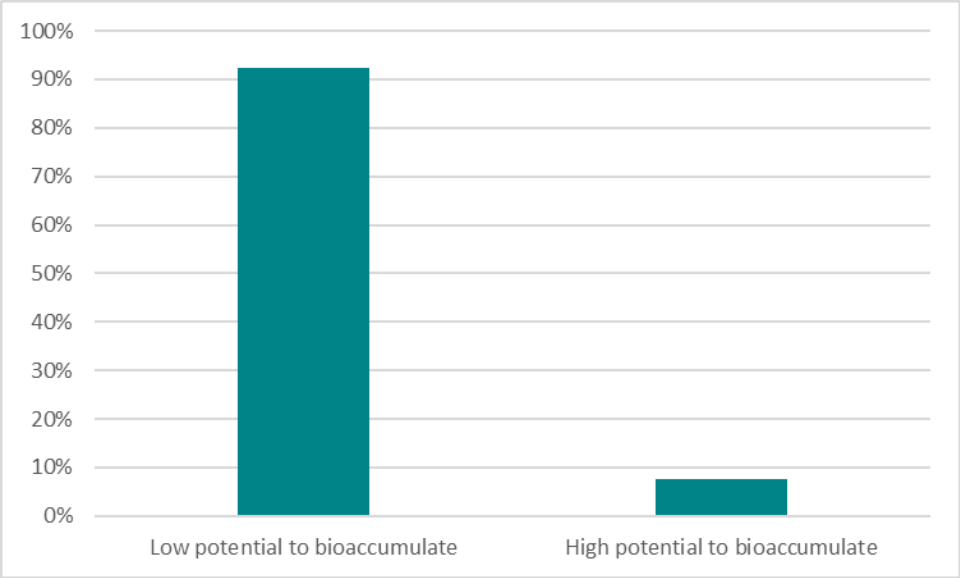

Figure 4. Outcome of the classification of potential for bioaccumulation at fass.se, assessed during 2022 (n=145).

3.4 Persistence

Of the 356 unique substances published at fass.se during 2022, 94 substances (26%) were classified for degradation, for 69 substances (19%) there were not sufficient data to classify them, and for 193 substances (54%), of which the majority were exempted substances, no hazard phrase was assigned.

In the assessment of degradability most of the substances, where a classification for degradation could be done, were assigned the phrase indicating that the substance is potentially persistent (62%) (Figure 5). Substances are classified as degradable e.g., if they have passed a ready biodegradability test (e.g. OECD 301) or sufficiently low dissipation half-lives are achieved in the OECD 308 test. Slowly degradable substances show either inherent degradability (e.g. OECD 302); pass the criteria set up for the OECD 308 test or show significant biotic or abiotic degradation in other tests. However, a classification that the substance is potentially persistent does not necessarily mean that it cannot be degraded in the environment, but that lack of sufficient data result in the classification persistent, or that persistence cannot be excluded. Substances within this category have failed a ready and/or inherent degradation test and/or the criteria established for the OECD 308 test. Substances within this category could also have been indicated to be potentially persistent, based on other standard or non-standard data.

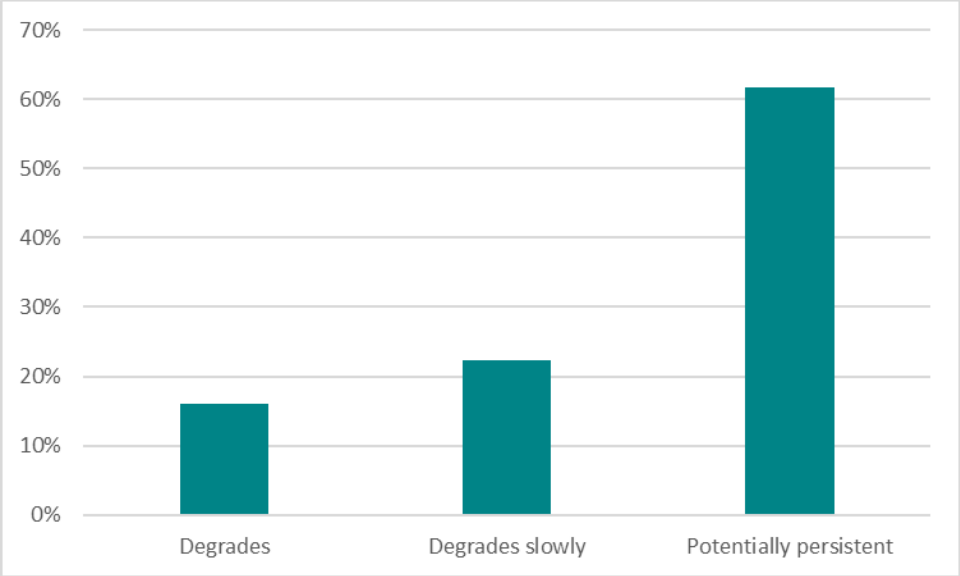

Figure 5. Outcome of the classification of degradation at fass.se for documents published during 2022 (n=94).

At the end of 2022 a total of 184 substances published at fass.se were classified as potentially persistent. 58 substances, in total, degrades slowly.

4 Future outlooks

During 2023 the FASS-project will continue to develop and strengthen the Swedish environmental classification system to make it a powerful tool on a national level and hopefully to raise acceptance and interest on an international level.

The work on improving the review process will continue with the aim to achieve a review process with no unnecessary delay in publication of the updated environmental risk assessments and to maintain a high quality and credibility of the published environmental information.

The Swedish system for environmental classifications of pharmaceutical products is quite uncommon, but the interest for this information is increasing. The assessment-team at IVL has participated in two interviews, performed by different research teams, which so far have resulted in a conference presentation (Schuitmaker-Warnaar, 2022) and a scientific publication (Linder, 2023). We believe that the demand for information about the environmental impact of pharmaceuticals will increase in the future, when both the public and the prescribers become increasingly aware of the impact of pharmaceuticals on the environment.

The European Commission regularly make updates and changes to the CLP regulation (Regulation EC No 1272/2008, on Classification, Labelling and Packaging of substances and mixtures), and during the spring 2023 new hazard classes for the classification of chemicals were introduced. The new hazard classes are:

- endocrine disruptors (ED) for human health or the environment
- persistent, bioaccumulative and toxic (PBT)
- very persistent and very bioaccumulative (vPvB)
- persistent, mobile and toxic (PMT)
- very persistent and very mobile (vPvM)

These new hazard classes may also eventually apply to the classification of pharmaceuticals. The current EMA guideline (EMA 2006), which was published in 2006, is not easy to interpret in all aspects, and since 2018 there is a draft update of the guideline. The draft describes in more detail how to assess e.g. an effect on development or reproduction (endocrine active substances, EAS) and performing a PBT assessment. The timeline for when the draft will be adopted and a new guidance will be published is not yet known, but it might be possible that the final

version will also include assessment of the mobility of the active ingredient. When the final version of the EMA guideline is published, the FASS guidance will most likely also need to be updated.

5 Reference list

Environmental classification of pharmaceuticals at www.fass.se. *Guidance for pharmaceutical companies.* 2012 v 3.0. Lif (2021).

Environmental classification of pharmaceuticals at www.fass.se. *Guidance for pharmaceutical companies 2007*. Lif (2007).

Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use. European Medicines Agency (EMA) (2006). Committee for Medicinal Products for Human Use (CHMP); 1 June 2006, Ref EMEA/CHMP/SWP/4447/00 Corr 2.

Draft guideline on the environmental risk assessment of medicinal products for human use – Revision 1. European Medicines Agency (EMA) (2018). Committee for Medicinal Products for Human Use (CHMP); 30 November 2018, Ref EMEA/CHMP/SWP/4447/00 Rev 1.

Schuitmaker-Warnaar, T. J. (2022*). 'Green Metrics' - Incorporating Environmental Dimensions In Health Technology Assessment.* Abstract from Health Technology Assessment international 2022 annual meeting, Utrecht, Netherlands.

Linder, E., Villén, J. *et al* (2023). *Stakeholders' perspectives and use of web-based knowledge support for environmental information on pharmaceuticals.* Exploratory Research in Clinical and Social Pharmacy, vol 11.

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This report has been reviewed and approved in accordance with IVL's audit and approval management system.