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Self-declarations of environmental classification at Fass.se

Experiences from the reviewing process during 2017

Lisette Graae, Emelie Westberg, Elin Belleza, Ann-Sofie Allard and Linda Örtlund

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Author: Lisette Graae, Emelie Westberg, Elin Belleza, Ann-Sofie Allard and Linda Örtlund, IVL Swedish Environmental Research Institute
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IVL Swedish Environmental Research Institute Ltd.
P.O Box 210 60, S-100 31 Stockholm, Sweden
Phone +46-(0)10-7886500 // www.ivl.se

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

Foreword

IVL Swedish Environmental Research Institute (IVL) has since 2005, with the launch of the system of self-declarations of environmental classification at www.Fass.se, conducted a project focused on review of the self-declarations financed by LIF - the Research-Based Pharmaceutical Industry in Sweden and the Foundation for IVL Swedish Environmental Research Institute (SIVL). This report describes the experiences gained during the review process in year 2017 and has been prepared with the aim to achieve transparency by explaining the role and the experiences of the reviewer, which may be useful in future development of the system. The main target groups are LIF and its member companies, as well as users of the environmental classifications, e.g. county councils and researchers.

Six previous reports describing experiences from the reviewing process have been published within the Fass-project. Lilja et al. (2013) describes the implementation of the environmental classifications of pharmaceuticals at Fass.se and the reviewing process from the project start in year 2005 until 2012. The other four reports, Andersson et al. (2013), Örtlund et al. (2014), Graae et al. (2015), Graae et al. (2016) , and Graae et al. (2017) each describe the reviewing process during the year prior to publication.

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Summary

Since 2005 Sweden has a unique environmental classification system for pharmaceutical products. It is a self-declaration system where each pharmaceutical company is responsible for their own environmental information. The environmental risk assessments are published on the web based portal www.Fass.se, which is open to the public. Prior to publication the environmental risk assessments 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 for the pharmaceutical companies. The present report describes the experiences from the review process during the year 2017. Data for the statistical analyses are gained both from the Fass.se database and from the "progression list", a spreadsheet the audit team uses to keep track of documents that have been reviewed or are under current review.

In 2017, 775 environmental risk assessments were sent in for review. Of these 46% received the comment no remarks and were recommended to be published. 33% received the assessment remark and were recommended to be corrected before publication and 21% needed to be corrected and sent in for another review before publication. The total number of unique substances that were published at Fass.se during 2017 was 478. Of these 28% were classified regarding environmental risk, 49% were exempted from classification and 23% were reviewed, but no classification could be made due to lack of data. Of the classified substances 83% received the assessment insignificant risk. One substance (Regorafenib) was classified as hazardous, two substances (Abiraterone acetate and Levonorgestrel) as posing high risk and seven substances (Desogestrel, Ethinylestradiol, Etonogestrel, Ibuprofen, Mycophenolic acid, Selenium sulphide, and Terbinafine) as posing moderate risk. 45% of the unique substances were assessed for bioaccumulation potential and 92% of these were classified with low potential for bioaccumulation. 29% of the unique substances were assessed for degradation and 68% of these were classified as potentially persistent.

The work of improving the review system is an on-going process. As a part of this work IVL Swedish Environmental Research Institute performs studies and activities to increase the knowledge of pharmaceuticals in the environment. During 2017 a two-year project started with the aim to develop, test and evaluate criteria for the implementation of a voluntary system for ERAs on pharmaceutical products, which would include carbon dioxide and API emissions along the entire lifecycle of pharmaceutical products, both at production and at formulation.

Sammanfattning

Sedan 2005 har Sverige ett unikt system för miljöklassificering av läkemedel. Systemet bygger på självdeklaration där varje läkemedelsföretag själva är ansvariga för miljöinformationen för sina substanser. Miljöklassificeringen publiceras på en web-baserad portal, www.Fass.se, som är öppen för allmänheten. Före publiceringen granskas miljödokumenten av IVL, som en oberoende extern part för att säkerställa att klassificeringarna baseras på en vetenskapligt accepterad tolkning av guiden som läkemedelsföretagen utgår ifrån. Utvärdering av systemet är en kontinuerlig pågående aktivitet och i föreliggande rapport beskrivs erfarenheterna från granskningsarbetet under 2017. Data för de statistiska beräkningarna kommer dels from Fass-databasen och dels från ”Levande listan”, som är ett Excelark granskarna använder sig av för att protokollföra vilka dokument som håller på att granskas och vilka som har granskats.

Under 2017 sändes 775 miljödokument till IVL för granskning. Av dessa rekommenderades 46 % direkt för publicering. Ytterligare 33 % fick rekommendationer för revidering innan publicering medan 21 % behövde korrigeras och återsändas för ytterligare granskning innan publicering. De statistiska beräkningarna av miljödokumenten i denna årsrapport baserar sig på de miljödokument som publicerades på Fass.se under år 2017. Totala antalet unika substanser var 478 och 28 % av dessa klassificerades med avseende på miljörisk. 49 % var undantagna från klassificering och 23 % blev granskade, men kunde inte klassificeras på grund av bristande information. 83 % av de klassificerade substanserna fick bedömningen försumbar risk. En substans (Regorafenib) klassificerades som särskilt miljöfarlig, två substanser (Abirateonacetat och Levonorgestrel) bedömdes medföra hög risk och sju substanser (Desogestrel, Etinylestradiol, Etonogestrel, Ibuprofen, Mykofenolacid, Selendisulfid och Terbinafin) bedömdes medföra medelhög risk för miljöpåverkan. För 45 % av de unika substanserna gjordes en bedömning av bioackumuleringspotential. 92 % av dessa klassificerades ha låg potential för bioackumulering. 29 % av de unika substanserna bedömdes med avseende på nedbrytning. Av dessa blev 68 % klassificerade som potentiellt persistenta.

Arbetet med att förbättra granskningssystemet är en pågående process. En del av detta arbete utgörs av studier och aktiviteter för att öka kunskapen om läkemedel i miljön. Under 2017 startade ett två-årigt projekt med syftet att utveckla, testa och utvärdera kriterier för införandet av ett frivilligsystem för miljöklassificering av läkemedelsprodukter, vilket skulle inkludera utsläpp av koldioxid och API längs läkemedelsprodukters hela livscykel både vid produktion och vid formulering.

1 Environmental classification of pharmaceuticals at Fass.se

1.1 Background

Pharmaceutical products are essential for health and wellbeing in our everyday life. Medicines provide enormous benefits, such as improvement in quality of life, and the demand will likely increase in the future due to a growing ageing population, chronic/lifestyle diseases, emerging market expansion, and treatment and technology advances. Unfortunately, benefits of the use of pharmaceuticals may come with an environmental downside. Therefore, pharmaceutical residues in the environment have become a prioritized area within environmental surveillance as well as within environmental risk assessment. It is a focus area in the EU Strategy for the Baltic Sea Region and it is being investigated in a number of national and international projects (see for example Halling-Sörensen B. et al. 1998, Fick J. et al 2011, Kümmerer K. 2004 and Medical Products Agency 2015).

In 2005 environmental information was published at Fass.se to test a new model for classification, developed on the initiative by LIF - The Research-Based Pharmaceutical Industry in Sweden. The initiative was a response to an increasing public demand for environmental information on pharmaceuticals and an attempt to develop a model accepted both by Swedish stakeholders, but also 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 model was developed by a Swedish Working Group consisting of LIF, the Stockholm county council, and the pharmacy chain Apoteket, the Swedish association of local authorities and regions (SKL) and the Swedish Medical Products Agency (MPA), in conjunction with the international pharmaceutical industry. During the implementation of this environmental classification system IVL Swedish Environmental Research Institute (IVL) runs projects with the aim to identify and address the pitfalls of the system. The Fass project is financed by LIF and the Foundation for IVL Swedish Environmental Research Institute (SIVL).

The results from the environmental classifications of pharmaceuticals are being presented at Fass.se, a web based pharmaceutical portal that includes information on all approved pharmaceuticals on the Swedish market. The information is accessible not only to experts, county councils and other purchasing actors, but open to the public as well. On the Swedish market today there are approximately 1900 active pharmaceutical ingredients (APIs) (MPA, January 2015, personal communication (Hillver S-E)).

The environmental classification at Fass.se is a self-declaration system meaning that each pharmaceutical company is responsible for the environmental information published at Fass.se. 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 for the pharmaceutical companies. The reviewing process ensures a common praxis for the implementation of the guideline among the different companies and feeds back experience from the self-declaration process to the system owners, LIF. At the same time the review of the classifications informs the companies on the needs in order for the environmental risk assessments

to be conducted according to the principles in the guideline (LIF 2012), in a scientifically acceptable way, 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. In the reviewing process, issues in need for further investigation are continuously coming up. This is due to availability of new data or knowledge in the field as well as possibilities of comparisons to be made across different pharmaceuticals with the same active ingredients. In order to keep its credibility it is thus of outermost importance 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 bases for the development of the reviewing process.

The overall aim of the Fass-project during 2017 was to continue to develop and strengthen the Swedish environmental classification system in order to make it a powerful tool on a national level and to raise acceptance and interest on an international level. This included continued review of the companies' interpretation of the guideline, with in depth discussions with LIF in cases where more guidance than the guideline contains was needed.

1.2 How the classifications are made

In the environmental classification of pharmaceuticals at Fass.se, the risk posed by the pharmaceuticals is differentiated in five different categories: insignificant risk, low risk, moderate risk, high risk and hazardous. In addition to the risk phrase, which concerns the risk of ecotoxicological effects, each substance is assigned hazard phrases for bioaccumulation and persistence. A substance can be exempted from classification, in accordance with the European Medicines Agency (EMA) Guideline (EMA 2006), if they are unlikely to result in significant risk to the environment, e.g. proteins, vitamins and electrolytes.

The environmental assessment at Fass.se is presented at two different levels. For the non-expert user there is a level with summary phrases describing the classifications regarding environmental risk, degradation and bioaccumulation, assigned to the substance. For the expert reader a second level includes all information that has been the basis for the self-declaration including a list of references to documents that have been used.

1.3 The guideline and the reviewing process

The guidelines to what environmental data that 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, SKL and 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 guideline was published in 2007 and a revised document was presented in June 2012.

Before publication of environmental data at Fass.se, the risk and hazard assessments are reviewed by IVL. IVL comments on the choice of classification phrase based on the supporting data and gives recommendations to LIF whether or not revision is needed by the company before publication. If revision is needed, the company is encouraged to send the risk assessment for another review before publication.

The review by IVL results in comments in four categories:

- **Major deviation** – deficiencies in the submitted material lead to an inaccurate classification of risk or/and 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 or/and hazard but still needs to be changed before publication at Fass.se
- **Remarks** – minor deficiencies, correction is recommended (although not mandatory) to be in full compliance with guideline
- **No remarks** – no deficiencies found in the submitted material and the document is recommended for publication.

2 Experiences from the reviewing process during 2017

2.1 Statistics of the review process during 2017

The audit team at IVL use a spreadsheet called the "progression list" as a tool to keep track of documents that have been reviewed or are under current review. The data recorded in the "progression list" is saved over time and extends back to October 2009. The statistic calculations presented here are based on data in the "progression list" for year 2017.

The total number of reviews during 2017 was 775 (taking into account that a company may send in documents for the same substance several times) and the most common assessment from IVL was to give no remarks (46%). During 2017, 624 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 (78%) of the environmental risk assessments got the comments "no remarks" or "remark". Only a minor part (22%) got a comment that needed to be corrected before publication. In total, risk assessments for 546 substances (lower than 624, since several companies may send in risk assessments for the same substance) were reviewed during 2017.

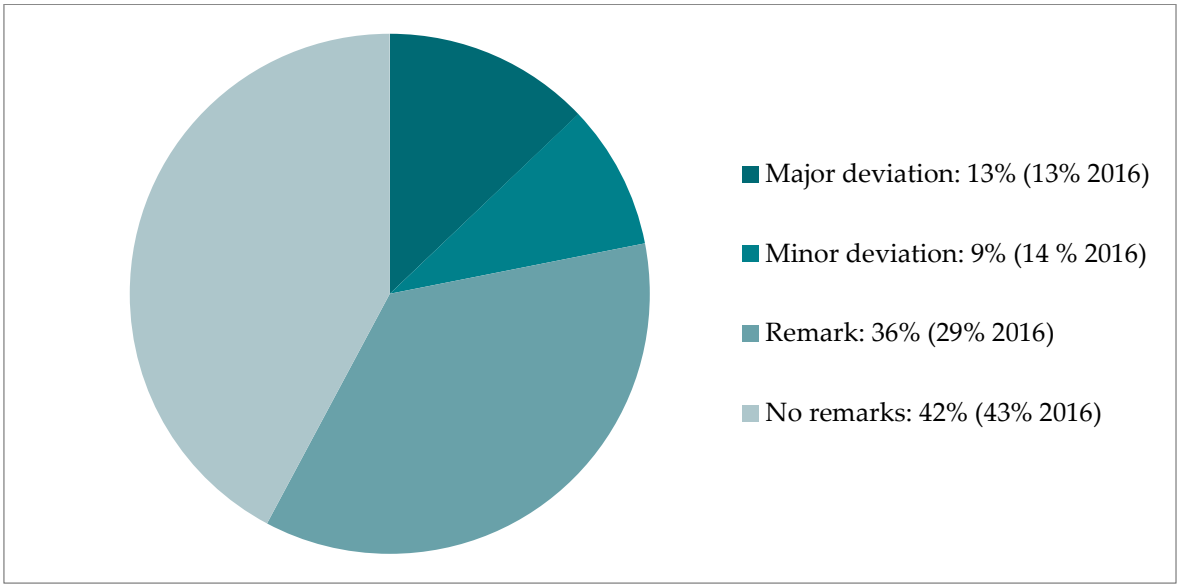

Figure 1: Distribution of the highest grade of recommendations that each company received for a specific substance that was sent in for review during 2017. The figure is based on the total number of reviews, i.e. 775 and the figure shows the highest grade of comment for each risk assessment during the year in the order: major deviation > minor deviation > remark > no remarks.

2.2 Development of the review process

Within the context as third party reviewer, IVL also performs related studies to increase the knowledge of pharmaceuticals in the environment and to develop and improve the reviewing process.

The environmental classification system on Fass.se is based on environmental risk-assessment (ERA) of individual active pharmaceutical ingredients (APIs). However, since the year 2007 and the discovery of emissions of high levels of pharmaceutical residues in effluents from drug manufacture (Larsson et al., 2007) the attention have shifted from only considering ERA of individual APIs to the full life-cycle of pharmaceutical products. As early as 2004 the Swedish Medical Products Agency (MPA), commissioned by the Swedish government, concluded in their report that APIs are of environmental importance and that an assessment should include the entire life cycle of the pharmaceutical product (The Dental and Pharmaceutical Benefits Agency (TLV), 2004). In 2011 the Swedish National Pharmaceutical Strategy (NPS) published a list of objectives to minimize the environmental impact of pharmaceuticals (NPS, 2011). One of the proposals was to encourage voluntary control of emissions from pharmaceutical factories by the introduction of a voluntary ERA of pharmaceutical products.

Therefore a two-year project started in 2017 with the aim to develop, test and evaluate criteria for a voluntary ERA on pharmaceutical products. The first part has been to develop environmental criteria for the API emissions. The second part has been to focus on life cycle assessment (LCA) and the use of natural resources during API-production and formulation. The third part will be to develop the model including both environmental criteria and LCA. The model will be discussed and evaluated together with stakeholders from the pharmaceutical industry to make sure that the model will be applicable to the pharmaceutical industries at large. The fourth part will be to

support the development and implementation of a new guideline for the introduction of a voluntary environmental assessment system of pharmaceutical products.

3 Final results of the classification

3.1 Environmental risk assessments included in the statistics

The statistics below are based on data from a document, generated by LIF, showing a snapshot of all the risk assessments that are published at Fass.se at the time the document is generated. The data is retrieved as close to the end of every year as possible in order to ease comparisons between each year's statistic calculations. The statistics include all the environmental risk assessments that had been published during 2016 and that could be viewed at Fass.se at 2017-01-02 (the date when the document was generated).

3.2 Environmental classification of substances

The total number of unique substances that was published at Fass.se during 2017 was 478, which corresponds to 531 environmental risk assessments. The larger number of risk assessments in comparison to the number of unique substances was due to the fact that one substance can be marketed and, thus, risk assessed by more than one company. 28% of the 478 unique substances were classified regarding environmental risk, 49% were exempted substances and another 23% were reviewed, but no classification could be made (either no data at all or not sufficient data). The distribution of the unique substances is illustrated in Figure 2, below.

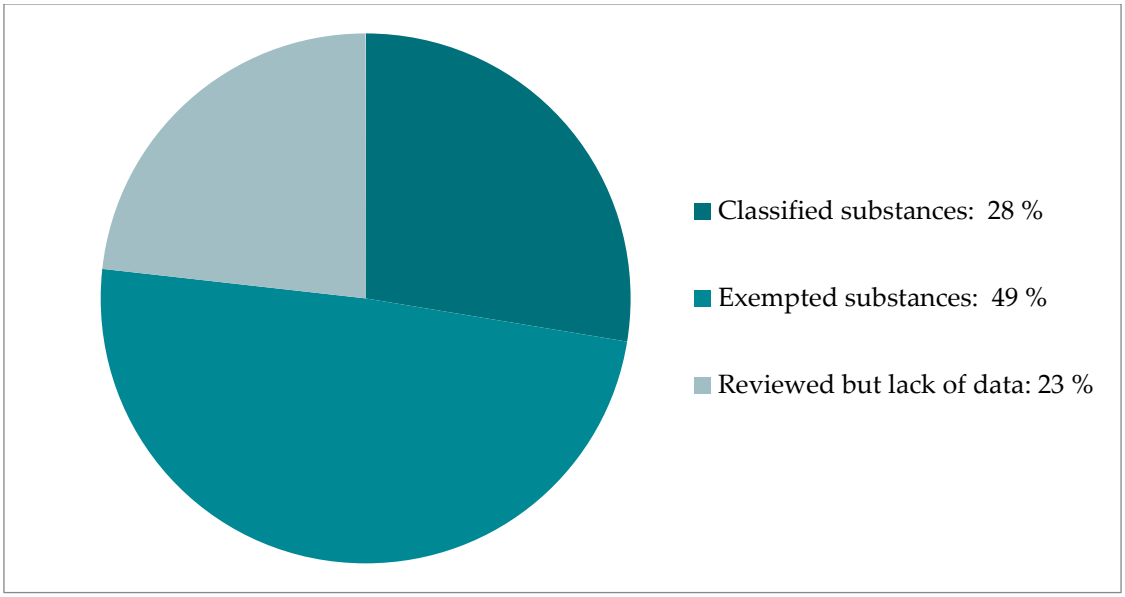

Figure 2: Outcome in terms of environmental classification of substances at Fass.se (n = 478). The figure covers classification of environmental risk, i.e. not potential for degradation or bioaccumulation.

3.3 Environmental risk

Of the 132 substances (28%) classified according to environmental risk the vast majority were classified as posing an insignificant risk (83%), 10% were classified as low risk, 5% as moderate risk, 2% as high risk and 1% as hazardous (Figure 3). A classification of an insignificant risk means that the PEC/PNEC ≤ 0.1, low risk: 0.1 < PEC/PNEC ≤ 1, moderate risk: 1 < PEC/PNEC ≤ 10 and high risk: PEC/PNEC > 10. When the PEC/PNEC < 1, but the substance is flagged as a potential PBT (Persistent, Bioaccumulative, and Toxic) or vPvB (very Persistent and very Bioaccumulative), the substance is classified as having hazardous environmental properties. The percentage of the substances classified as posing a moderate risk was 25%, substances classified as posing a high risk was 2% and substances with hazardous environmental properties was 1%.

Two substances were published during 2017 and classified as posing a high risk; Abiraterone acetate (used in the treatment of prostate cancer) and Levonorgestrel (used in a number of birth control methods). One substance was published during 2017 that was classified as hazardous; Regorafenib (used for cancer treatment). Seven substances were published during 2017 and classified as posing a moderate risk; Desogestrel, Ethinylestradiol and Etonogestrel (hormone treatments, commonly used as birth control), Ibuprofen (nonsteroidal anti-inflammatory drug), Mycophenolic acid (immunosuppressant drug used to prevent rejection in organ transplantation), Selenium disulphide (used to treat pityriasis versicolor, seborrheic dermatitis, and dandruff) and Terbinafine (antifungal medication used to treat ringworm, pityriasis versicolor, and fungal nail infections).

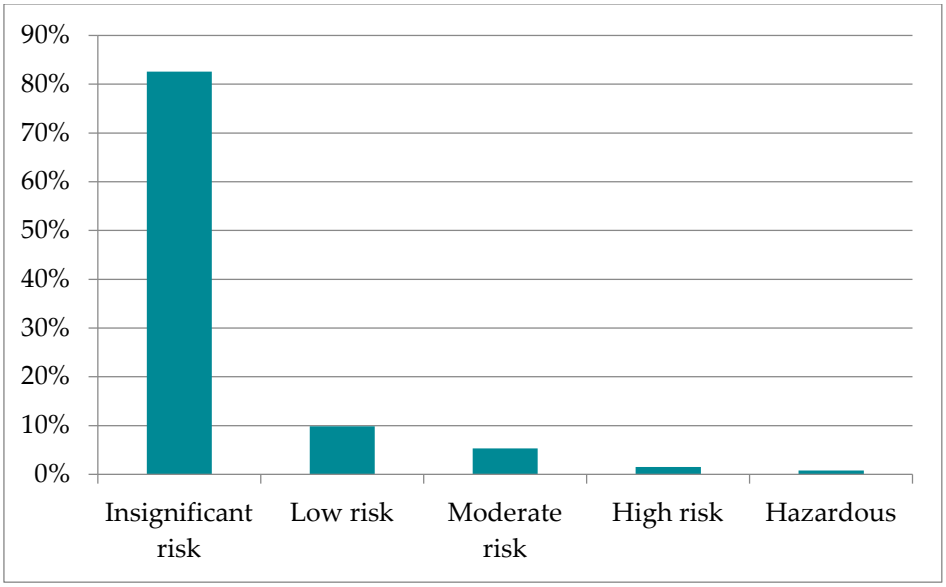

Figure 3: Outcome of the environmental risk assessments of pharmaceuticals at Fass.se (n = 132).

3.4 Potential to bioaccumulate

Of the 478 unique substances published at Fass.se during 2017, 215 (45%) were assessed for bioaccumulation potential. For 27 substances (6%) data to make an assessment were not available and for 236 substances (49%) a hazard phrase was not assigned. The majority of the latter were exempted substances, for which an assessment of bioaccumulation potential was not made.

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

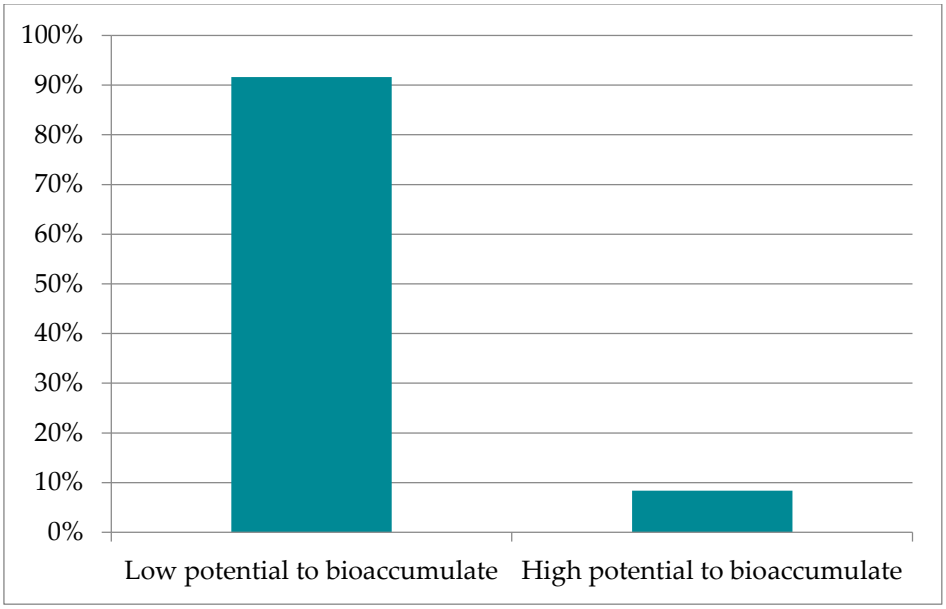

Figure 4: Outcome of the classification of bioaccumulation at Fass.se (n = 215).

3.5 Persistence

Of the 478 unique substances published at Fass.se during 2017, 138 substances were classified for degradation (29%), data for classification were lacking for 104 substances (22%) and for 236 substances (49%), of which the majority were exempted substances, no hazard phrase was assigned.

In the assessment of degradability the majority of the substances classified for degradation were assigned the phrase indicating that the substance is potentially persistent (68%) (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 e.g. 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 persistence or that persistence cannot be excluded. Substances within this category have failed a ready and/or inherent degradation test and/or the criteria proposed 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.

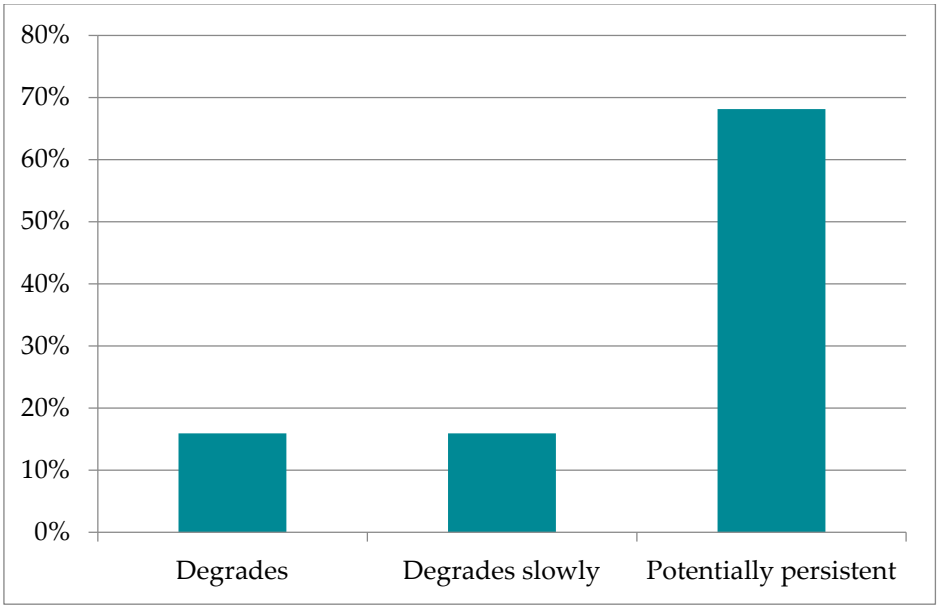

Figure 5: Outcome of the classification of degradation at Fass.se for documents published during 2017 (n = 138).

4 Future outlook

During 2018 the Fass.se-project will continue to develop and strengthen the Swedish environmental classification system in order to make it a powerful tool on a national level and to raise acceptance and interest on an international level. This will be achieved by two activities:

1. Continued review of the companies' interpretation of the guideline, with in depth discussions with LIF in cases where more guidance than the guideline contains is needed. During the review process the content and implementation of the guideline (LIF 2012) is continuously evaluated and discussed within the review team at IVL and between LIF and IVL. The results of these discussions will be inputs when the guideline is updated.
2. The environmental classification system at Fass.se is based on environmental risk assessment of individual APIs. To further develop the ERA of pharmaceutical products, a two-year study to develop, test and evaluate a model for environmental assessment on pharmaceutical products along their entire life-cycle is carried out. The project started in 2017 and will continue in 2018. The first part has been to develop environmental criteria for the API emissions. The second part has been to focus on life cycle assessment (LCA) and the use of natural resources during API-production and formulation. The third part will be to develop the model including both environmental criteria and LCA. The model will be discussed and evaluated together with stakeholders from the pharmaceutical industry to make sure that the model will be applicable to the pharmaceutical industries at large. The fourth part will be to support the development and implementation of a new guideline for the introduction of a voluntary environmental assessment system of pharmaceutical products.

5 Concluding remarks

- The Fass-project has now been on-going for twelve years and has resulted in a unique collection of environmental risk assessments for pharmaceutical substances, accessible to experts, county councils and other purchasing actors, as well as the public via the web-based portal www.Fass.se.
- IVL has given feedback to LIF regarding the system as such, both from a scientific perspective as well as from a quality assurance perspective, providing possibilities to evaluate and improve the system.
- In the review of the classifications IVL has informed the companies, via LIF, on the revision needs, in order for the environmental risk assessments to be conducted according to the principles in the guideline (LIF 2012), in a scientifically acceptable way, thus supporting the quality and credibility of the system.
- 775 risk assessments (pre-published) were checked in for review during 2017. 46% of these received no remarks and were recommended to be published; a large part of these were however substances exempted for classification. The remaining risk assessments received comments with recommendations for revisions.
- The work with 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.
- The statistic calculations of the environmental risk assessments are based on data from a document, generated by LIF, showing a snapshot of all the risk assessments that are published at Fass.se at the time the document is generated. The statistics in this report include all the environmental risk assessments that have been published during 2017 and that could be viewed at Fass.se at 2018-01-10 (the date when the document was generated).
- Risk assessments for 478 unique substances were published at Fass.se during 2017. 28% of the unique substances (n = 132) were classified regarding environmental risk; 49% were exempted from classification and 23% were reviewed, but no classification could be made due to lack of data.
- A majority of the classified substances (83%) received the assessment insignificant risk. One substance (Regorafenib) was classified as hazardous, two substances (Abiraterone acetate and Levonorgestrel) as posing high risk and seven substances (Desogestrel, Ethinylestradiol, Etonogestrel, Ibuprofen, Mycophenolic acid, Selenium sulphide, and Terbinafine) as posing moderate risk.
- 45% of the unique substances (n = 215) were assessed for bioaccumulation potential. 92% of these were assigned a hazard phrase indicating low potential to bioaccumulate (i.e. log K_{ow} < 4, according to the Fass guideline (2012)).
- 29% of the unique substances (n = 138) were assessed for degradation. 68% of these were assigned a phrase indicating that the substance is potentially persistent.
- During 2017 a two-year project started with the aim to develop, test and evaluate criteria for the implementation of a voluntary system for ERAs on pharmaceutical products, which will include carbon dioxide and API emissions along the entire lifecycle of pharmaceutical products.

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IVL Swedish Environmental Research Institute Ltd.
P.O. Box 210 60 // S-100 31 Stockholm // Sweden
Phone +46-(0)10-7886500 // www.ivl.se