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Self-declarations of environmental classification at Fass.se

Experiences from the reviewing process during 2018

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Preface

IVL act as an independent and external reviewer of environmental information that pharmaceutical companies use for environmental classification of pharmaceutical products. The report describes the experiences from the review process during the year 2018.

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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, which is published on the open web-based portal www.Fass.se. Prior to publication the environmental risk assessments are reviewed by IVL Swedish Environmental Research Institute (IVL) as an independent, external part. The present report describes the experiences from the review process during the year 2018. Data for the statistical analyses are gained both from the Fass.se database and from a spreadsheet that the audit team develop and use to keep track of documents that have been reviewed or are under current review.

In 2018, 373 environmental risk assessments (ERAs) were sent in for review. Almost 60% of the reviewed assessments received the comment no remarks and were recommended to be published, whereas the other 40% were recommended or needed to be corrected before publication. The number of unique substances that were published at Fass.se during 2018 was 361. Of these substances a little more than half of them were exempted from classification, one fourth were classified regarding environmental risk, and the rest quarter could not gain any classification due to lack of data.

The work of improving the review system is an on-going process. As a part of this work IVL performs studies and activities to increase the knowledge of pharmaceuticals in the environment. In 2018/2019 a model was developed for environmental assessment of pharmaceutical products, in regard to environmental risks related to emissions of Active Pharmaceutical Ingredient (API) from production processes and product carbon footprint in a life cycle perspective. The proposed model is aimed to deliver product specific environmental assessment results that may be used in different applications to control, manage and reduce impacts along the pharmaceutical value chain and drive improvements in different parts of the chain.

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. Denna rapport beskriver erfarenheterna från granskningsarbetet under 2018. Data för de statistiska beräkningarna kommer dels from Fass-databasen och dels från ett excelark granskarna använder sig av för att protokollföra vilka dokument som håller på att granskas och vilka som har granskats.

Under 2018 sändes 373 miljödokument till IVL för granskning. Av dessa rekommenderades nästan 60 % direkt för publicering. De återstående 40% rekommenderades att eller behövde korrigeras innan publicering. Antalet unika substanser som publicerades på Fass.se under 2018 var 361. Drygt hälften av dem var undantagna klassificering, en fjärdedel klassificerades med avseende på miljörisk och ytterligare en fjärdedel kunde inte klassificeras beroende på otillräckliga data.

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 2018/2019 utvecklades och föreslogs en modell för miljöbedömning av läkemedelsprodukter med avseende på miljörisker relaterade till utsläpp av aktiv läkemedelssubstans (API) från produktionsprocesser samt klimatavtryck i ett livscykelperspektiv. Den föreslagna modellen levererar produktspecifika resultat från miljöbedömningar som kan användas på olika sätt för att kontrollera, styra och reducera miljöeffekter längs värdekedjan för läkemedel, och för att driva förbättringsarbete i olika steg i kedjan.

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 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 2018 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. It also included developing and proposing a model for environmental assessment of pharmaceutical products, that includes both environmental risks from emissions of Active Pharmaceutical Ingredients (API) and carbon footprint in a life cycle perspective.

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 (LIF 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 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 2018

2.1 Statistics of the review process during 2018

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 2018.

The total number of reviews during 2018 was 373 (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 (59%). During 2018, 322 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 (90%) of the environmental risk assessments got the comments "no remarks" or "remark". Only a minor part (10%) got a comment that needed to be corrected before publication. In total, risk assessments for 310 substances (lower than 322, since several companies may send in risk assessments for the same substance) were reviewed during 2018.

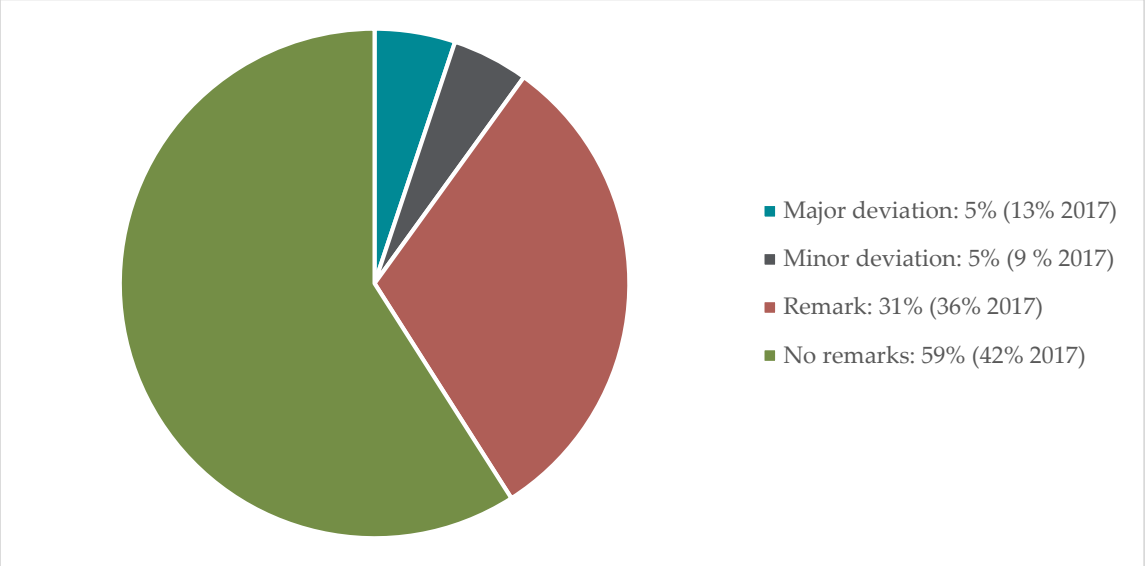

Figure 1: Distribution of the highest grade of recommendations that each company received for a specific substance that was sent in for review during 2018. The figure is based on the total number of reviews, i.e. 373 and the figure shows the highest grade of comment for each risk assessment during the year in the order: major deviation > minor deviation > remark > no remarks.

2.2 Development of the environmental assessment

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.

There is an increased focus and awareness of the environmental consequences of pharmaceuticals. So far much of the attention has been directed towards the environmental consequences of emissions of active pharmaceutical ingredients (API), both regarding emissions associated with residues reaching the environment subsequent to human ingestion and excrement, and emissions from production of the APIs. There is, however, a growing awareness that also other environmental aspects along the pharmaceutical life cycle should be considered, such as climate impacts, resource depletion and other local environmental impacts. A number of studies and strategies have been published highlighting the need for common models and criteria to assess, report and evaluate the environmental impacts of pharmaceutical products for different applications, in order to be able to prioritize and promote actions to control and reduce the impacts.

As a response to this need of information, a two-year project was initiated with the objective to develop and propose a model for environmental assessment of production of pharmaceuticals, that includes two parts:

- Environmental risk assessment (ERA) of emissions of API from local production.
- Carbon footprint of pharmaceutical products in a life cycle perspective.

During 2018 the model was developed and discussed with different stakeholders from the pharmaceutical industry, primarily pharmaceutical companies. The sub-project was finalized in mid-2019 and the proposed model is described in a separate project report. The ERA part of the model builds on the current environmental classification at Fass.se, where some calculations have been updated to reflect local emissions from production rather than emissions after use. The carbon footprint part of the model covers greenhouse gas emissions in a life cycle perspective. To secure comparability and verifiability, we propose to use the framework described in ISO 14025 for environmental product declarations and initiate the development of Product Category Rules (PCR) for pharmaceutical products.

The proposed model is aimed to deliver product specific environmental assessment results that may be used in different applications to control, manage and reduce impacts along the pharmaceutical value chain and drive improvements in different parts of the chain. The project report includes an overview of potential use of the information by different stakeholders, such as pharmaceutical benefits subsidy systems, procurement, process and product improvement, guidance in product choice as well as assessments in conjunction with product approval.

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 2018 and that could be viewed at Fass.se at 2019-01-09 (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 2018 was 361, which corresponds to 405 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. 24% of the 361 unique substances were classified regarding environmental risk, 56% were exempted substances and another 20% 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.

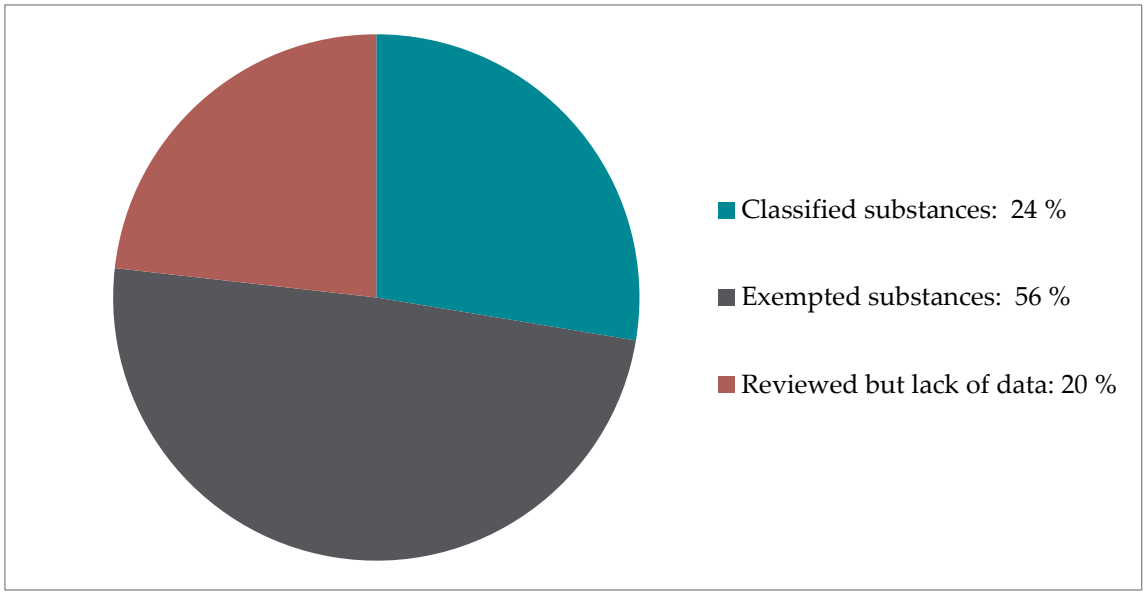

Figure 2: Outcome in terms of environmental classification of substances at Fass.se (n = 405). The figure covers classification of environmental risk, i.e. not potential for degradation or bioaccumulation.

3.3 Environmental risk

Of the 86 substances (24%) classified according to environmental risk the vast majority were classified as posing an insignificant risk (85%), 6% were classified as low risk, 5% as moderate risk, 3% 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.

One substance published during 2018 was classified as hazardous: Bedaquiline, an antibiotic used in treatment of multi-drug-resistent tuberculosis. Three substances were classified as posing high risk: Ciprofloxacin (an antibiotic used to treat a number of bacterial infections), and Estradiol and Etinylestradiol (hormone treatments, commonly used as birth control). Four substances published during 2018 were classified as posing moderate risk: Chlorhexidine (a disinfectant and antiseptic used for skin disinfection before surgery and to sterilize surgical instruments), Mycophenolic acid (an immunosuppressant antibiotic drug used to prevent rejection in organ transplantation), Norethisterone (hormone treatment, commonly used as birth control), and Terbinafine (an antifungal drug used to treat fungal nail infections and ringworm).

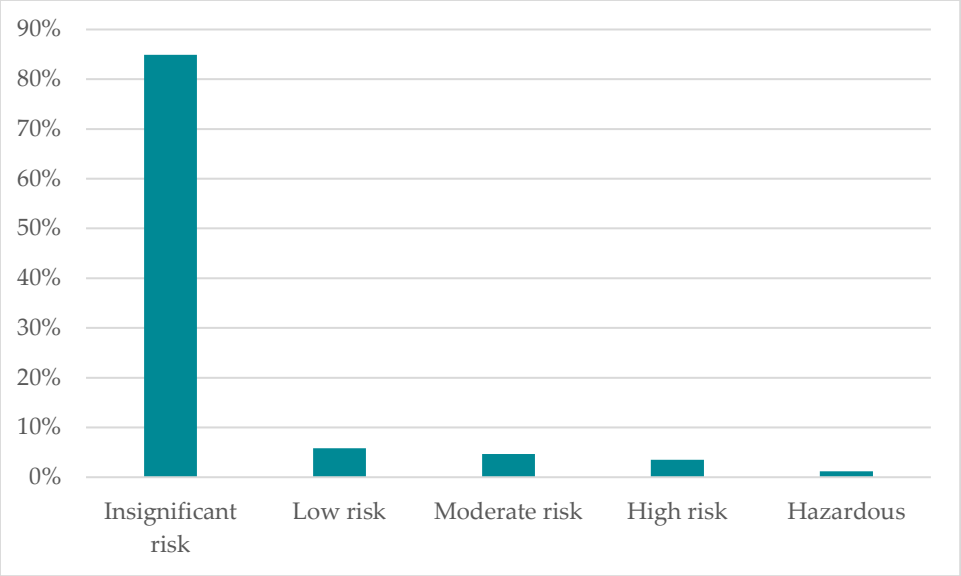

Figure 3: Outcome of the environmental risk assessments of pharmaceuticals at Fass.se (n = 86).

3.4 Potential to bioaccumulate

Of the 361 unique substances published at Fass.se during 2018, 132 (37%) were assessed for bioaccumulation potential. For 26 substances (7%) data to make an assessment were not available and for 203 substances (56%) 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 (89%). 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.

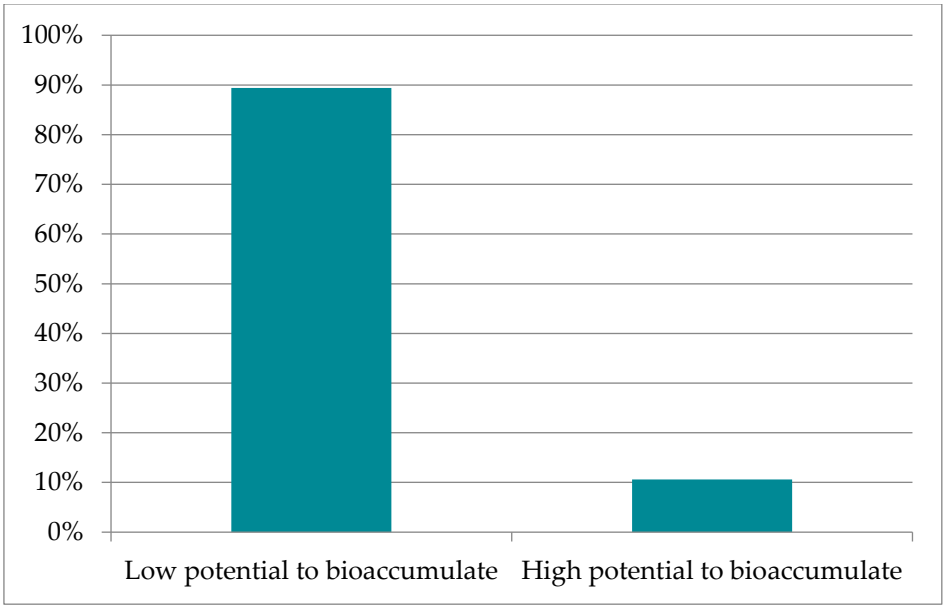

Figure 4: Outcome of the classification of bioaccumulation at Fass.se (n = 132).

3.5 Persistence

Of the 361 unique substances published at Fass.se during 2018, 87 substances were classified for degradation (24%), data for classification were lacking for 71 substances (21%) and for 203 substances (56%), 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 (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 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.

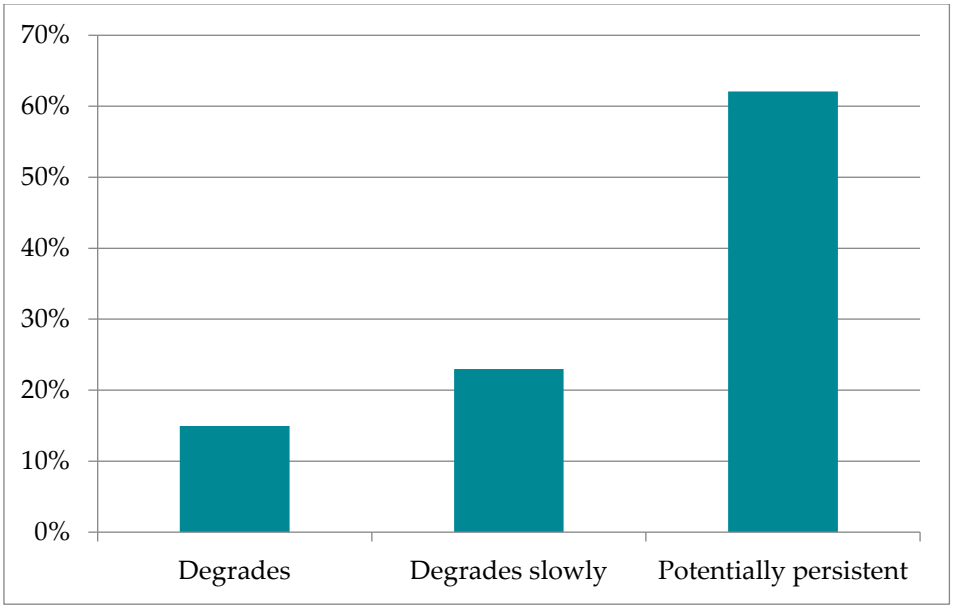

Figure 5: Outcome of the classification of degradation at Fass.se for documents published during 2018 (n = 87).

4 Future outlook

During 2019 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. In the development of the proposed model for environmental assessment of pharmaceutical products, that includes environmental risks related to Active Pharmaceutical Ingredients (API) and carbon footprint in a life cycle perspective, it was identified that the actual intended application of results needs to be better understood in order to prioritise and guide further development and implementation of the model. Therefore, the objective for the follow-up work, which will start mid-2019, is to define and evaluate needs, requirements and use of product specific environmental information by different stakeholders along the pharmaceutical value chain. This will be done through a system and actor analysis, which is aimed to result in:
   a. A mapping of roles and responsibilities in the work to reduce impacts along the chain, including where and how the information can be used to prioritize, measure and follow-up improvements, as well as identification of knowledge and competence requirements to use the information in a correct way.
   b. An overview of drivers, incentives and barriers for reporting and using product specific environmental information in different parts of the value chain.

5 Concluding remarks

- The Fass-project has now been on-going for fourteen 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.
- 373 risk assessments (pre-published) were checked in for review during 2018. 59% 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 2018 and that could be viewed at Fass.se at 2019-01-09 (the date when the document was generated).
- Risk assessments for 361 unique substances were published at Fass.se during 2018. 24% of the unique substances (n = 86) were classified regarding environmental risk; 56% were exempted from classification and 20% were reviewed, but no classification could be made due to lack of data.
- A majority of the classified substances (85%) received the assessment insignificant risk. One substance (Bedaquiline) was classified as hazardous, three substances (Ciprofloxacin, Estradiol and Etinylestradiol) as posing high risk and four substances (Chlorhexidine, Mycophenolic acid, Norethisterone and Terbinafine) as posing moderate risk.
- 37% of the unique substances (n = 132) were assessed for bioaccumulation potential. 89% of these were assigned a hazard phrase indicating low potential to bioaccumulate (i.e. log K_{ow} < 4, according to the Fass guideline (2012)).
- 25% of the unique substances (n = 87) were assessed for degradation. 62% of these were assigned a phrase indicating that the substance is potentially persistent.
- During 2018/2019 a model for environmental assessment of pharmaceutical products was developed and proposed, that includes both environmental risks from emissions of API from production processes and carbon footprint in a life cycle perspective. The proposed model was discussed with representatives from the pharmaceutical industry and is presented in a separate project report.

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