CWPharma

CLEAR WATERS FROM PHARMACEUTICALS

Enhanced environmental permitting of pharmaceutical plants in the Baltic Sea region

Authors:

Ülle Leisk, Vallo Kõrgmaa / Estonian Environmental Research Centre (EERC), Estonia

Jeppe Bregendahl / Kalundborg Utility, Denmark

Ville Junttila, Lauri Äystö & Jukka Mehtonen / Finnish Environment Institute (SYKE), Finland

Jan Schütz, Michael Stapf / Berlin Center for Competence of Water (KWB), Germany

Anete Kubliņa, Intars Cakars / Latvian Environment, Geology and Meteorology Centre (LEGMC), Latvia

Anna Dworak, Radosław Walkowiak / Institute of Environmental Protection - National Research Institute (IOS), Poland

Kristina Nyhlén, Jill Lindstam / County administrative board of Östergötland (CAB), Sweden

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Introduction

This report aims to identify good practices for environmental permitting of pharmaceutical plants in some Baltic Sea (BS) countries and spread them to other countries where they are lacking or inefficient. The objective is to enhance permitting of pharmaceutical plants within current legislation framework to obtain information on their active pharmaceutical ingredient (API) emissions to municipal WWTPs (MWWTPs) and environment, resulting in improved information on pharmaceutical emissions, and aiding with direct mitigation measures when necessary.

The pharmaceutical industry is highly globalized, interconnected and heterogeneous both spatially and temporally. The pharmaceutical industry includes API-production and the production of pharmaceutical products. Emissions from these activities may vary significantly. Also, as many activities are patch processes, emissions of specific substances are likely to happen only sporadically. The pharmaceutical industry may also include (re)packaging and other activities.

The UNESCO & HELCOM Status Report on Pharmaceuticals (2017) [1] contains some information on pharmaceutical production in Estonia, Finland and Sweden, but no information on permitting practices of pharmaceutical plants. Thus, this report fills in identified information gaps related to the production of pharmaceuticals, e.g. by HELCOM.

The working method evaluates the current national practices for environmental permitting for pharmaceutical plants in all seven countries represented in the project CWPharma (Denmark, Estonia, Finland, Germany, Latvia, Poland and Sweden) with the aim of collecting some information also from Russia.

In the Baltic Sea region (BSR), wide recommendations on good practices for environmental permitting of pharmaceutical plants are proposed to initiate the process that clarifies the role of the pharmaceutical industry as a possible source of APIs and to estimate the need for measures that control the pharmaceutical industry's emissions.

Additionally, the aim is to evaluate the industrial wastewater contracts between municipal wastewater treatment plants (MWWTPs) and pharmaceutical plants in each BS country, even if this task is more difficult than the task related to environmental permitting of pharmaceutical plants. These documents are not publicly available, and thus the information on contracts proved difficult to obtain. The BSR wide recommendations are aimed at formulating good practices for industrial wastewater contracts between MWWTPs and pharmaceutical plants.

The activities of this report pose very high transnational relevance in the Baltic Sea region (i.e. transnational spreading of good practices), because the recommendations are based on the current good practices in BSR countries and improvements made for them. Furthermore, the objective is that the recommendations will be utilised and implemented in all Baltic Sea countries.

The information presented in this report will be used to identify priority measures at a national level to reduce pharmaceutical emissions. The results will also increase knowledge among target groups under the CWPharma project (pharmaceutical industry, operators of MWWTPs, permitting

and supervisory authorities) and other relevant stakeholders through national stakeholder meetings and reports.

1. Overview of environmental legislation relevant for the pharmaceutical industry

Active Pharmaceutical Ingredients (APIs) are based on organic molecules that have been synthesized and modified to provide medicinal products and comprises the largest segment of available drugs [2]. Manufacturing of pharmaceutical products could be defined as the chemical synthesis, fermentation, extraction, formulation and finishing of pharmaceutical products and, where these are carried out at the same site – as the manufacturing of intermediate products [3].

1.2. EU legislation

Several environmental regulations are important, regarding the environmental emissions from manufacturing sites. The most relevant regulations for APIs emission reductions to the water environment are Industrial Emissions Directive, Water Framework Directive and Urban Waste Water Treatment Directive.

Industrial Emissions Directive

One of the main aims of the directive 2010/75/EU (Industrial Emissions Directive -IED) is to ensure the prevention and control pollution. Each installation should only operate if it holds a permit or is registered - which is in the case of certain installations and activities using organic solvents [3]. Production of pharmaceutical products, including intermediates, has been listed as an activity subject for IED (Articles 10 and 56) [3]. Although IED generally requires permits from production units with certain capacity, it does not define the chemical industry's threshold values. Annex I only specifies that activities contained in section four have production on an industrial scale by chemical or biological processing. The absence of quantitative values in Annex I has been justified by the European Commission, reasoning that the scale of chemical manufacturing can vary from a few grams (of a highly specialized product), to many tonnes (of a bulk chemical product). Yet, both may correspond to "industrial scale" for their particular activities [4]. While defining "industrial scale", the European Commission also recommends taking into account following criteria [4]:

- The nature of the product
- The industrial character of the plant and machinery used
- Production volume
- Commercial purpose
- Production solely for own use
- Environmental impact

Such considerations should take account of the primary objective of the IED as expressed in Article 1 as to "prevent or, where that is not practicable, to reduce emissions into air, water and land and to prevent the generation of waste to achieve a high level of protection of the environment taken as a whole", This is complemented by the general principle set in Article 11 (c) that, "no significant pollution is caused". Still, it remains a responsibility for the competent authorities to make an informed and justified judgment on whether a particular installation falls under the scope of the IED [4].

The IED also outlines that permit conditions for production facilities falling under the IED scope must be set based on of the best available techniques (BAT) [3]. Three documents are relevant to the pharmaceutical sector:

- Reference Document on Best Available Techniques for the Manufacture of Organic Fine Chemicals [21]
- Best Available Techniques (BAT) Reference Document for the Production of Large Volume Organic Chemicals [5]
- BAT Guidance Note on Best Available Techniques for Pharmaceutical and Other Speciality Organic Chemicals [6]

Water Framework Directive

One of the ultimate aims of the directive 2000/60/EC (Water Framework Directive – WFD) is the elimination of priority hazardous substances and the achievement of near background concentrations for naturally occurring substances in the marine environment. Pollution through the discharge, emission or loss of priority hazardous substances must cease or be phased out. Based on the proposal from the Commission, the European Parliament and Council should agree on the substances to be considered as a priority for action. Specifically, measures must be taken against polluted water by those substances, taking into account all significant sources and identifying cost-effectiveness, proportionate levels and a combination of controls [7].

Two directives under WFD set out environmental quality standards (EQSs) concerning the presence of certain substances or groups of substances in surface water, identified as priority pollutants because of the significant risk they pose to or via the aquatic environment:

- Directive 2008/105/EC sets EQSs for 33 priority substances and 8 other pollutants.
- Directive 2013/39/EU updated the EQSs for 7 of the 33 original priority substances and included 12 newly identified priority substances. Directive 2013/39/EU also required the Commission to establish a Watch List (WL) of substances for which EU-wide monitoring data are to be gathered to support future prioritization exercises.

The WL ((EU) 2015/495, (EU) 2018/840 and (EU) 2020/1161) is a list of potential water pollutants that should be carefully monitored by the EU member states to determine the risk they pose to the aquatic environment and whether EQS should be set for them. This list should be updated every two years [8].

The first WL was published in 2015 and it included 10 substances or groups of substances, including macrolide antibiotics erythromycin, clarithromycin and azithromycin, one synthetic (EE2) and two natural hormones (E1 and E2) and the anti-inflammatory drug- diclofenac. This list was reviewed in 2018 and in 2020. Diclofenac was removed from the list and two antibiotics, amoxicillin and ciprofloxacin, were added in the first revision [9]. In the second revision, the hormones and macrolide antibiotics were removed from the list. Simultaneously, sulfamethoxazole, trimethoprim, venlafaxine and its metabolite O-desmethylvenlafaxine and several azole compounds (e.g. clotrimazole, fluconazole and miconazole) were included into the list.

Urban Waste Water Treatment Directive

An objective of the directive 91/271/EC (Urban Waste Water Treatment Directive - UWWD) [10] is to protect the environment from adverse effects of urban waste water discharges and discharges from certain industrial sectors. UWWD defines the industrial wastewater (Article 2), sets requirements for pretreating industrial wastewater entering collection systems (Annex Ic), and

requires pre-authorization (Articles 11-13) of all discharges of urban wastewater, of discharges from the food-processing industry and of industrial discharges into urban wastewater collection systems.

Environmental risk assessment in the context of marketing authorization of pharmaceutical products'

Under Article 8(3) of Directive 2001/83/EC [11], as amended, the evaluation of the potential environmental risks posed by the use of medicinal products shall be submitted. The environmental impact of active pharmaceutical ingredient shall be assessed in the context of marketing authorization, and on a case-by-case basis, specific arrangements to limit this impact shall be considered [12]. One of the key legislative factors influencing the presence of the APIs in the environment is the current framework for environmental risk assessment (ERA), which is a part of the market authorisation (MA) process [12, 13, 14] Similar to new chemicals introduced to the EU markets, assessment for persistency, bioaccumulation and toxicity (PBT) potential must be determined for all APIs whose predicted environmental concentrations exceed 0.01 μg/L. In case of veterinary medicinal products, the environmental risk may be accounted for in the marketing authorization. However, there is no specific guidance available on how to include the PBT assessment in the risk-benefit analysis or on which risk management measures should be taken. For human medicinal products, the PBT assessment's output is not accounted for in the risk-benefit analysis and may not be used as the grounds for rejection of the MA; it has not resulted in any tangible consequences [13] to date.

1.3. National legislations and practices in EU countries

In BSR countries, the permitting of pharmaceutical industry can be divided into two general categories – integrated permits and other permits (single-medium permits). While other permits can control certain emission individually, an integrated permit is required for the installation's operation as a whole. Integrated environmental permits replace ambient air pollution permit, waste permit and permit for the special use of water [15]. It also means that regulators must set permit conditions for achieving high level of protection for the environment as a whole [11]. Usually, BAT concept is used to balance benefits to the environment as large against the operator's costs. In this way, integrated permitting attempts to prevent waste generation and emissions and, where that is not feasible, reduce them to acceptable levels [16].

According to the findings from the Interreg Baltic Sea Region project BEST- Better Efficiency for Industrial Sewage Treatment [17] the legislation on industrial wastewater discharge into municipal wastewater systems at the EU is in place in most of the BSR countries - at national and regional levels. However, the implementation of such laws presents challenges, mainly due to the authorities' political will to protect the industrial organisations and local businesses. Also, insufficient knowledge by water utilities and industrial organisations on industrial wastewater characteristics and its influence on the municipal wastewater system and receiving water bodies leads to a failure to protect the environment more effectively [17].

Market authorization and environmental permitting are adopted in all BSR countries from EU regulations (integrated permits are used also in Russia). Still, there are some significant differences between EU countries, either on enforcing the regulations or by the regulatory system itself. All BSR EU countries have adopted IED to their regulations, but integrated permits are not used for all industrial facilities. The legislation for permitting of pharmaceutical industries in BSR EU countries is described in chapter 3.1.

1.4. Russian Federation legislation

The Russian Federation is a nation with a federal system of government consisting of republics, regions, federal cities, autonomous regions and autonomous districts that are equal "subjects" of the Russian Federation. Republics have their own constitutions and legislation [18].

Federal legislation sets out the fundamentals of regulation in the sphere of health care. Federal Law on Pharmaceuticals No. 86-FZ of June 22, 1998 (as amended on December 18, 2006) (the Pharmaceutical Law) establishes the general framework of legal requirements applicable to the circulation of pharmaceuticals, including development, production, trials, quality control, efficacy, safety, importation and sale. Given its importance to the public health care sector for providing the population with safe and high quality pharmaceuticals, the Pharmaceutical Law makes it a priority for the state to control the production, quality, efficacy, and safety of pharmaceuticals [18].

Production of pharmaceuticals may be carried out by manufacturers that have a license for the production of pharmaceuticals. It is prohibited to produce pharmaceuticals in the following cases:

(i) pharmaceutical is not registered in the Russian Federation, except those intended for clinical trials
(ii) without a license for production
(iii) violation of the rules of production and quality control approved by the Ministry of Health.

Production of patented pharmaceuticals and their sale is performed in compliance with patent and trademark legislation. State control over the production of pharmaceuticals is carried out by the Federal Health Service, which is entitled [18]:

(i) to have free access to the manufacturer's facilities and to take samples of produced pharmaceuticals
(ii) to make copies of documents necessary for pharmaceuticals quality control
(iii) prohibit production of pharmaceuticals and sale of finished pharmaceuticals that were forbidden by the rules of production and quality control.

Russia's state environmental policy is designed to ensure the protection, reproduction and sustainable use of its natural resources as the prerequisites for a healthy and safe environment. The right of Russian citizens to a healthy environment is guaranteed by the Constitution of the Russian Federation [19]. The requirements specified in the EU Directive and the HELCOM Recommendations are also reflected in Russian legislation [17]. The main amendments regarding water management issues have been in force since January 1, 2019 [17]

Integrated environmental permits are issued to legal entities and sole traders operating category I environmentally hazardous facilities. One permit must be issued for each separate facility which has a negative impact on the environment, including a linear facility following an the operator's application. Legal entities and sole traders engaged in economic and (or) other activities at category II facilities shall be entitled to receive an integrated environmental permit if there are relevant industry technical manuals on best available technologies. The permit is issued by the territorial body of Rosprirodnadzor following a positive conclusion of the state environmental impact assessment of the materials justifying the permit. The permit is issued for seven years and can be extended for another seven years under the conditions set by the Federal Law of 10.01.2002 N 7-FZ "On Environmental Protection". The permit is subject to revision in full or in part if changes in the production of the technological processes, equipment, and raw materials entail a change in the established volumes or mass of emissions, discharges or waste disposal limits [20]. The concept

of the best available techniques (BAT) and their application issues are specified in Federal Law No. FZ-7 of January 10, 2002, on Environmental Protection [17].

Local authorities approve the standards (originally calculated by water utilities) for wastewater volume discharged from industries. These standards are based on the capacity of a central sewerage system for wastewater treatment and transportation, and the conditions set by the water utility. According to the national legislation, the relationship between a water utility and an industrial enterprise is regulated by a contract (for water disposal only or water supply and disposal jointly). These contracts are standardized, and their form was approved by Decree of the Russian Federation Government. Yet, if the contract is supplemented with personal or commercial data, it becomes confidential. Permitting authorities are not authorised to evaluate the contracts in regard to industrial wastewater [17].

2. Overview of pharmaceutical industry in the BSR

2.1. Overview of the intensity of pharmaceutical production and processing in the BSR

Europe is the second biggest pharmaceutical market globally. In 2017, North America accounted for 48% of sales compared to 22% in Europe, 7.7% in Japan, 5.1% in Latin America and 17% for Asia, Africa and Australia [21]. Asia has major API production, although pharmaceutical products may be produced and sold elsewhere.

The pharmaceutical industry is a major industrial asset to the European economy, strongly research-based and one of the best performing high technology sectors. Europe produces more than 40% of the world's pharmaceutical output by value, which still makes it the world's leading manufacturing location ahead of the US (over 30%) and Japan (20%) [2]. During 2013–2017, 77 new chemical or biological entities were marketed in Europe, compared to 100 in United States, 30 in Japan and nearly 39 entities in rest of the world [21].

Although the biggest pharmaceutical production markets are located in Germany, France, Italy, Spain and United Kingdom, the market share of BSR countries is about 20% of total European pharmaceutical production (in 2016 the total European pharmaceutical production was 250 million euros) [22]. In 2017, the pharmaceutical industry invested an estimated 35 billion euros in research and development (R&D) in Europe with an average market growth of 4.4% for the total European market [21]. R&D is in high regard in the BSR region, as BSR countries contribute about 24% of European R&D investments.

The pharmaceutical industry directly employs *ca* 750 000 people in Europe and more than 190 000 people in the Baltic Sea countries, and indirectly employs about 2.3–3.0 million people in Europe [22].

2.2. Pharmaceutical production in Baltic Sea catchment area

The total number of pharmaceutical plants that produce APIs within the Baltic Sea catchment area is difficult to estimate for several reasons:

- IED has not been implemented/interpreted similarly in all BSR countries and it does not give any threshold values for pharmaceutical industry. Due to the lack of definition of "industrial scale" and an absence of quantitative values in Annex I has been justified by the European Commission [4] with reasoning that of chemical manufacture can vary from a few grams (of a highly specialized product) to many tonnes (of a bulk chemical product). It seems that both pharmaceutical companies and authorities have been interpolating an obligation for environmental permitting differently in various countries. As a result, several production facilities have an obligation for integrated permits without permits (see chapter 3,1).
- Reporting obligation to E-PRTR database is dependent on the pollutant emission quantities and/or amount of the transfer hazardous waste off-site.
- EudraGMDP database contains numerous entries that are not valid anymore (e.g. production facilities that have changed ownership) or are not relevant in the context of pharmaceutical production (e.g. companies distributing pharmaceuticals).

All available data, from public databases and company's' websites, were gathered and analyzed to map pharmaceutical production facilities in the Baltic Sea catchment area,.

Pharmaceutical production plants according to E-PRTR database

According to E-PRTR Regulation [23], each chemical facility that fulfils following criteria has to report data to the E-PRTR database (https://prtr.eea.europa.eu/#/home):

- The facility falls under at least one of the 65 E-PRTR economic activities that are listed in Annex I of the E-PRTR Regulation; it exceeds at least one of the E-PRTR capacity thresholds.
- The facility's transfer of off-site waste exceeds specific thresholds set out in Article 5 of the Regulation.
- The facility releases pollutants that exceed specific thresholds specified for each media - air, water and land - in Annex II of the E-PRTR Regulation.

In 2016, 82 facilities with activities within NACE code C21 (Manufacture of basic pharmaceutical products and pharmaceutical preparations) were listed in the E-PRTR database. In 2017, this number was 85. Table 1 shows the number of pharmaceutical plants within the Baltic Sea catchment area and Figure 1 shows their distribution in the BSR.

Table 1. The number of pharmaceutical production facilities in the Baltic Sea catchment area reporting to E-PRTR database.

Country	2016	2017
Denmark	11	12
Estonia	0	0
Finland	5	5
Germany*	5 (42)	5 (42)
Latvia	2	2
Lithuania	0	0
Poland	13	15
Sweden	9	9
Total	45	48

* In Germany the number in parentheses shows the total number of reporting facilities.

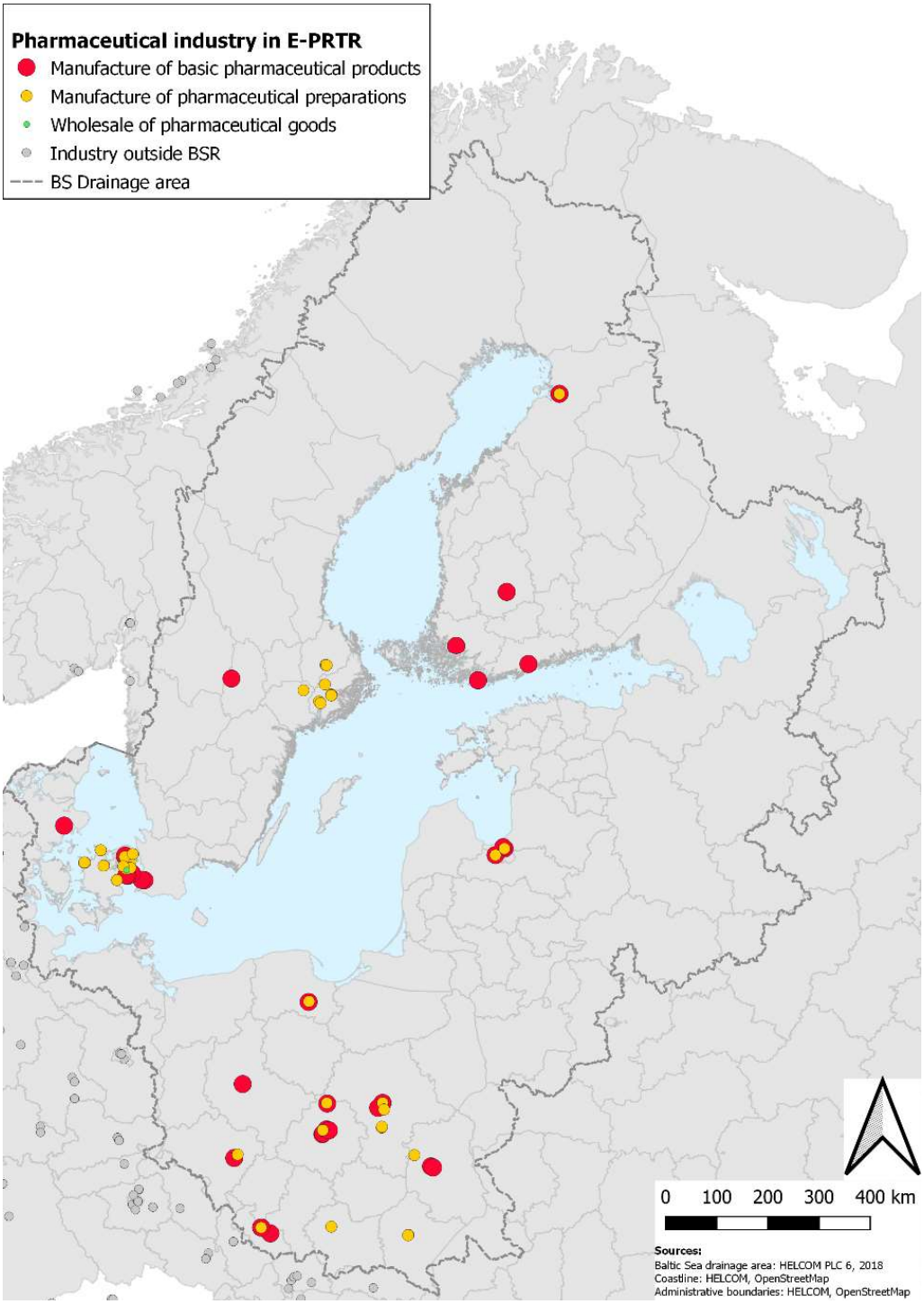

Figure 1. Pharmaceutical plants within the Baltic Sea catchment area according to the E-PRTR database

Pharmaceutical production plants according to EudraGMDP database

The EudraGMDP database (http://eudragmdp.ema.europa.eu/inspections/logonGeneralPublic.do) is the Community database on manufacturing, import and wholesale-distribution authorisations, good manufacturing-practice (GMP) and good-distribution-practice (GDP) certificates [21].

In October 2020, there were 647 companies with Manufacturing and Importation Authorization (MIA) and 2468 companies that held a Good Manufacturing Practice (GMP) within the Baltic Sea catchment area.

Table 2. The number of pharmaceutical production facilities in the Baltic Sea catchment area reporting to the EudraGMDP database.

Country	Companies with Manufacturing and Importation Authorization (MIA)	Companies with a Good Manufacturing Practice (GMP)
Denmark	146	1226
Estonia	24	28
Finland	34	70
Germany	15 (1646)	91 (2125)
Latvia	34	55
Lithuania	24	27
Poland	244	739
Russia*	0	38
Sweden	126	194

*Russia does not recognize GMP certificates issued by regulatory authorities of other countries and regions, e.g. EU, only local GMP certificates are authorised [24].

3. Environmental permitting of pharmaceutical plants

3.1. General information about environmental permits issued in BSR countries

Two different permitting approaches are used for the countries in the Baltic Sea region (Figure 2). While all countries use integrated permits for pharmaceutical plants subject to IED, the approach of smaller facilities differs. For IED plants it is expected (and/or demanded) that BATs are implemented. On the other hand, smaller installations may be partially permitted (single-medium permits), or may receive an integrated permit without being obligated to implement BAT.

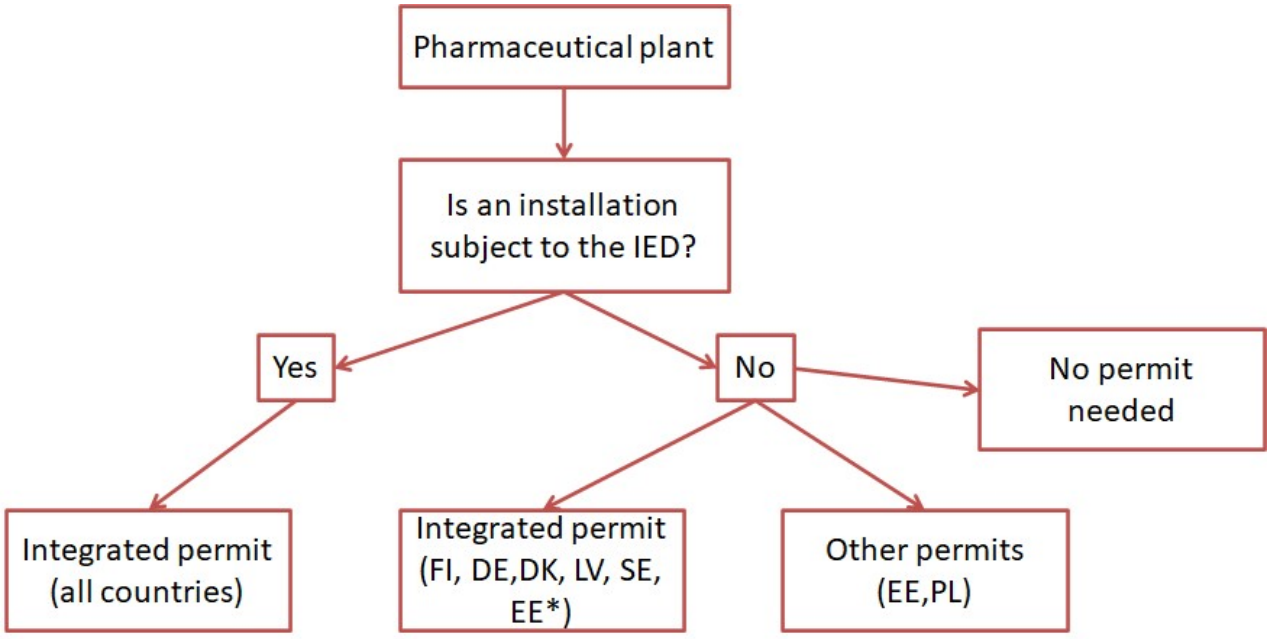

Figure 2. Generalisation of permitting regulations in BSR countries.

The difference between integrated permits and single-medium permits could be described as:

- **An integrated environmental permit** is issued to operate industrial plants with a high pollution potential in a way that ensures the least possible impact on the environment and human health. The integrated environmental permit is actually combination of permits that replace individual environmental permits - a special permit for water use, a waste permit and an ambient air pollution permit [15]. It also means that regulators must set permit conditions to achieve a high level of protection for the environment as a whole [16]. The environmental impact is considered comprehensively so that one indicator should not lead to the deterioration of others. For example, reduction of air emissions must not lead to an increase in waste generation or discharges [25, 26]. It also means that regulators must set permit conditions to achieve a high level of protection for the environment as a whole. These conditions are commonly based on the BAT concept, which balances the benefits to the environment against operator costs [16].
- **A single-medium permit** is issued to deal with specific environmental problems (e.g. emissions to ambient air). These permits could be given out to control certain emission individually. Generally, the purpose is to protect human health or some element of the

ecosystem. This is essentially an “end-of-pipe” regulation, and it does not address the design and operation of industrial facility as a whole system to minimize emissions [16].

The overall goal of environmental permitting is for regulatory authorities to define (in a transparent and accountable manner) legally binding requirements for individual sources of significant environmental impact to protect human health and the environment [11] Usually, the BAT concept is used to balance environmental benefits against operator costs. By way of this concept, integrated permitting attempts to prevent waste generation and emissions and, where that is not feasible, to reduce them to acceptable levels [11].

Each CWPharma partner collected information about permitting practices in their own countries, focusing on APIs in the pharmaceutical industry.

Denmark

In Denmark, the pharmaceutical production falls under the general Executive Order of the Environmental Protection Act. The act regulates all activity that "through emissions of solid, fluid or airborne substances, through emissions of microorganism, can be of damaging to the environment or health, or through the generating of waste can cause pollution of air, water, solid or underground."[27]. All companies and production that fall under this definition are required to apply for an environmental permit. All changes in production or increases in production volume are also required to apply for a new environmental permit.

The environmental permit is divided into two categories:

- **The first category** comprises of companies or productions that have a substantial emission potential. Under this category, companies are required to fulfil all the requirements set by the IED, including BAT conclusions and a mandatory baseline report. The companies in category one must make use of all relevant BATs as defined in the 2010/75/EU. Each company must prove to the authorities that BAT has been implemented, before the environmental permit can be granted.
- **The second category** includes all companies that require environmental permit after national regulations. The companies in the second category do not exhibit the same kind of emission potential as category one, and the application process is simplified and does not require the same amount of documentation. Companies are not obliged to use BAT, but have to document - to the authorities- that the technology they used prevents emissions.

Whether the company is regulated either by the municipality or the national environmental protection agency (which is the authorised authority), depends on its emission levels. The authority is obliged to ensure that the company upholds the regulations and BAT technologies. The authority can perform unannounced checks and must have access to all documentation and data.

In Denmark, all applications for an environmental permit must go through "Construction & Environment" which will distribute the application to the relevant authority, which is either the municipality or Environmental Protection Agency. The company will be classified as either Category 1 or Category 2 production — depending on the size of production, type of emissions, location, or type of resources.

Eight out of the twenty-eight sectors/activities fall under Category 1, and the other twenty falls under Category 2. Each sector/activity is expressed by a set of standard term, which help in making application process more streamlined and predictable. The standard terms are setup by the Environmental Protection Agency, with the assistance of the municipality and relevant sectors. A

company can thereby know which of the sectors/activities they fall under and also what kind of regulations they would be obligated to uphold.

The pharmaceutical industry falls under Category 1. Companies under Category 1 are obliged to uphold all BAT-conclusions set forward by the 2010/75/EU.

Apart from the environmental permit, an environmental assessment must also be carried out. The environmental assessment is carried out by the municipal authorities. The environmental assessment takes local and regional natural resources into account. The emissions associated with production are evaluated, and initiatives are taken to minimize the emissions. The environmental permit is also done to assess whether the production/project is in violation with the Espoo-convention, and therefore should not be permitted.

Estonia

According to the Estonian Medicinal Products Act [28] medicinal products may be manufactured only by the holder of an activity license for the manufacture of medicinal products. The act defines the manufacture of medicinal products, including intermediate products, as the sterilization, packaging, labeling, re-packaging, re-labeling and quality control of medicinal products, and the release of batches together with related procuring, receipt, storage and dispensing of materials.

An activity license for the manufacture of medicinal products is required for the total or partial manufacture of medicinal products, including for making active substances of medicinal products and investigational medicinal products, as well as for partial manufacturing operations, including the replacement of the safety features of packaging, i.e. means allowing for identification of packaging and means for preventing package tampering.

An activity license for the manufacture of medicinal products is not mandatory if the activities are carried out by the holder of an activity license of general pharmacy, hospital pharmacy or veterinary pharmacy either for the preparation of medicinal products as magistral formulae in accordance with a medical prescription, officinal formulae or for dividing-up into retail packaging for dispensing. An activity license for the manufacturing of medicinal products is not mandatory for the manufacturing of investigational medicinal products if the packaging, labelling, repackaging or, re-labelling of the medicinal products is carried out in a hospital pharmacy, and the medicinal products are used exclusively in the hospital operated by the person who produced the hospital pharmacy.

The holder of an activity license for the manufacturing of medicinal products must ensure that the active substances of medicinal products are manufactured and distributed in compliance with the good manufacturing and distribution practices based on Articles 47(3) and (4) of Directive 2001/83/EC of the European Parliament and of the Council on the Community Code relating to medicinal products for human use (OJ L 311, 28.11.2001, pp. 67–128). To verify it, the holder of the activity license for the manufacturing of medicinal products must carry out audits at the sites of operation of the manufacturers and distributors of the active substances for human use. An audit may be outsourced from a third party but it does not affect the responsibility of the holder of the activity license for manufacture. All activity licenses are accessible in the Estonian Agency of Medicines' database for activity licenses [29] and EudraGMDP database [21].

An environmental permit is an authorization issued by the Environmental Board, which grants the developer the right to use natural resources (e.g. water, minerals, etc.), to generate pollutants (e.g. waste gases) and waste. There are various environmental permits: an integrated environmental permit, ambient air pollution permit, a special permit for the use of water, a waste permit, general

geological research permit, geological exploration permit, permit for extraction of mineral resources and permit for radiation.

In Estonia, the Directive 2010/75/EU on industrial emissions is transposed to the Industrial Emissions Act [2] which states that (§ 16) no installation or combustion plant, waste incineration plant or waste co-incineration plant shall be operated without a permit, except for operators who are subject to registration provided for in Chapter 5 of this Act (installations using organic solvents). According to the Industrial Emissions Act (§ 19), an integrated permit is required in the chemical industry.

Still, there are no environmental permits issued for the pharmaceutical industry. Six pharmaceutical plants in Estonia are subject to IED as chemical industry plants, and one pharmaceutical facility has an environmental permit on other basis (permit for ambient air as company owns a boiler house). . Although there are at least six production facilities in Estonia that are subject to IED, it should be noted that none of them has an environmental permit (except for an ambient air permit for a boiler house owned by one of the companies).

Finland

The Pharmaceutical Act (LL, 395/1987) regulates the production of pharmaceuticals. The purpose of the Act is to maintain and develop safety of pharmaceuticals and their production and ensure the proper production and availability of medicines.

The industrial production of pharmaceuticals is allowed only in the factories approved by the Finnish Medicines Agency (Fimea). The production facilities and devices must follow the requirements set in the LL. The non-industrial production of pharmaceuticals for pharmacies' own sales (so-called extempore products) is also possible when Fimea is notified. Approximately 50% of Finnish pharmacies produce extempore products. When applying for permission from Fimea, the producer must deliver documents required by the LL.

According to the LL, principles and instructions given in the EU directive 2001/83/EC must be followed when pharmaceuticals are produced industrially and also where applicable production is done non-industrially. Granting of concession requires that EU's instructions concerning good practices for the manufacturing and distribution of pharmaceuticals (GMP) are followed. Only active ingredients which are produced and distributed in accordance with the GMP shall be used.

The demand of environmental permit for pharmaceutical industry is set in the Environment Protection Act (YSL, 527/2014) and Environmental Protection Decree (YSA, 713/2014). Regulations for industrial emissions and waste management are set in the YSL and the Waste Act (JL, 646/2011). Also, regulations concerning the handling and storage of chemicals used in pharmaceutical industry are set in the chemical safety legislation (390/2005, VNa 685/2015, VNa 856/2012).

The Finnish Environmental Protection Act lists activities (YSL, Annex 1) that require an environmental permit. The Annex contains two lists, and one of the lists contains activities that require an environmental permit according to IED (75/2010/EU), while the other one lists the activities that require an environmental permit on other bases. According to the current legislation (YSL, 27§), the pharmaceutical industry is required to have an environmental permit if any of the conditions listed below applies:

1. The plant is considered an IED-plant.

2. The plant uses more than 50 tons of organic solvents per year.
3. The activities in the plant can cause water pollution.
4. Wastewater management in the plant can cause pollution to receiving small water bodies (e.g. ditches) or springs.
5. The activities in the plant can place excessive strain on neighbours — in the form of contaminants, dust, smell, noise, radiation, or other similar emissions.

The Finnish Environmental Protection Act was renewed in 2014. As a result, the permit threshold for the pharmaceutical industry was increased. According to the repealed Environmental Protection Act (YSL2000, 86/2000), the pharmaceutical industry was categorically required to have an environmental permit. All of the current environmental permits issued to pharmaceutical production facilities that are located in Finland have been permitted according to YSL2000. As the permit threshold was increased, permits for the facilities not requiring permits according to the current YSL have been voided (YSL 231 §).

In a recent Finnish study [30], the environmental permits issued to 13 pharmaceutical production facilities located in Finland who were producing either medicinal products or pharmaceutically active ingredients were examined. Special attention was given to how pharmaceuticals emitted in wastewaters and wastes were considered in the environmental permits and specifically in permit conditions. In general, it was observed, that the pharmaceutical industry is seldom required to monitor the pharmaceutical emissions generated in their activities or the impacts their emissions may have on the environment. Nevertheless, according to the current YSL, industrial operators must be aware of their environmental impacts (YSL 6 §) and limit their emissions into the environment and the sewer network to the lowest level possible (YSL 7 §). Nearly all examined factories (twelve out of the thirteen plants) lead their waste waters into the municipal sewer network after pretreatment or after separating the most harmful fractions for further treatment. The three most recently issued permits included explicit considerations for pharmaceuticals emissions in wastewaters.

Germany

The German Medicines Act (AMG) serves as the legal basis for the protection of the health of the population, in particular, due to the high demands on the care in dealing with pharmaceuticals by the pharmaceutical industry, pharmacists and doctors. This mainly concerns the topics of production, marketing, testing, prescribing, information and dispensing of pharmaceuticals (AMG 1976). According to AMG, medicinal products may be manufactured, prepared, imported and distributed only by holders of an activity license issued by the federal or local authorities (§ 13 AMG 1976). According to § 16 AMG, the applicant is granted the activity approval for a certain production site as well as for certain medicinal products and dosage forms. When changing or expanding the production of medicinal products, a new activity license must be issued (§16 AMG 1976).

In 2006, the "Regulation on the production of active ingredients and pharmaceuticals" (AMWHV) was introduced, which, among other things, transposed the European directives 2001/20/EC, 2001/82/EC and 2001/83/EC into national law. Under this Regulation, the holder of an activity license for the manufacture of medicinal products must ensure that the active ingredients of medicinal products are manufactured and distributed in accordance with the Good Manufacturing Practices (GMP) (AMWHV 2006).

According to the "Federal Emission Control Act" (BImSchG) and the "Fourth Ordinance for the Implementation of the Federal Emission Control Act" (4. BImSchV) in conjunction with Article 10 and Annex I of Directive 2010/75/EU, manufacturers of pharmaceuticals and pharmaceutical intermediates are required to admit their installation to the national or regional authorities if they produce medicinal products by chemical, biochemical or biological conversion on an industrial scale (BImSchG , 4. BImSchV). Excluded are installations that serve exclusively for the manufacturing of the dosage form (4. BImSchV).

In Germany, the introduction of the European Industrial Emissions Directive (2010/75 / EU) in the year 2010 had a major influence on the legislation of the "Federal Emission Control Act" (BimSchG), the Water Resources Act (WHG) and the Circular Economy Act (KrWG) and other regulations e.g. “TA-Luft” and “BimSchV”. The “Federal Emission Control Act” (BImSchG) is the most important practice-relevant set of rules for the protection of humans, animals, plants, soils, waters, atmospheres and cultural assets against emissions. According to BimSchG, there are two categories for the operation of an installation:

- **Installations requiring permitting:** Installations requiring permitting are installations that can pose a particular environmental burden, danger or nuisance to the general public and neighbourhood. The installations that require permitting are named in Annex 1 of the 4th BImSchV.
- **Installations not requiring permitting:** No approval is required for installations in the research, development or testing of new ingredients, fuels, products or processes on a laboratory or pilot plant scale (§ 1 (6) of the 4th BImSchV).

The operation of installations for the manufacture of medicinal products by chemical, biochemical and biological conversion and their intermediates on an industrial scale falls under category 1. There is no definition of “industrial scale” at present; it can be decided on a national level. For an integrated environmental permit, operators of installations for the manufacture of medicinal products must comply with the provisions of the "Federal Emission Control Act" (BImSchG) and the "Fourth Ordinance for the Implementation of the Federal Emission Control Act" (4th BImSchV) in conjunction with Article 10 and Annex I of Directive 2010/75/EU.

Latvia

According to Pharmaceutical Law, medicinal products may be manufactured only by the holder of a special permit (license). A license is also needed for the preparation, importing and distribution of medicinal products. The purpose of Pharmaceutical Law is to regulate the activities of natural and legal persons in the field of pharmaceuticals, as well as to ensure the manufacture and distribution of medicinal products which are qualitative, medically appropriate, and of an appropriate prophylactic, treatment and diagnostic level.

According to Cabinet Regulation No. 304 ”Regulations Regarding the Procedures for the Manufacture and Control of Medicinal Products, the Requirements for the Qualification and Professional Experience of a Qualified Person and the Procedures for the Issuance of the Certificate of Good Manufacturing Practice to a Medicinal Products Manufacturing Undertaking” (18.04.2006), license for the manufacture of medicinal products is required for both total and partial manufacturing processes, as well as for different dividing up, packaging and presentation processes of a finished product. A license is not required for a pharmacy in which a pharmacist prepares and divides up, as well as changes the packaging or presentation of medicinal products intended for individual patients on prescription by a medical practitioner (formula magistralis) or a written

request by a medical institution, or for medicinal products which are manufactured according to the pharmacopoeia monographs and which are intended for distribution to the patients served by the relevant pharmacy (formula officinalis).

List of manufacturers, importers and distributors of active pharmaceutical substances that are registered in Latvia is available in European Union united data base EudraGMDP. It is also published on the homepage of the State Agency of Medicines of the Republic of Latvia (Farmaceitiskās darbības uzņēmumu reģistrs, n.d.) [31].

An environmental permit is an administrative act issued by the State Environmental Service that allows performing a polluting activity, on the condition that the equipment or part of it functions per the requirements specified in normative acts of environmental protection (Cabinet Regulation No. 1082 "Procedure by which polluting activities of category A, B and C shall be declared and permits for the performance of category A and B polluting activities shall be issued" (30.11.2010)) and Law On Pollution. There are various types of environmental permits: Category A or B permit for the performance of polluting activities, notification regarding the performance of Category C polluting activities, permits for the emission of greenhouse gases, permit for the use of water resources, licenses for the use of subterranean depths; permits for collection, transport, reloading, sorting or storage of waste; licenses for activities with sources of ionising radiation.

In Latvia, environmental permits do not contain limit values for indirect wastewater discharges. Thus, the environmental authorities leave it for the water utilities to define any restrictions for the quantity or quality of wastewater in the industrial wastewater contracts with industrial operators (Project BEST, 2020).

From the eight producers of API (EudraGMDP database), except those that produce only plant tinctures and oxygen, four of the producers have environmental permits – three have category A permits ("NORTHERN SYNTHESIS", "Olainfarm", "GRINDEKS") and one has a category B permit ("RĪGAS FARMACEITISKĀ FABRIKA").

From the eleven importers of API (those importers that produce only plant tinctures and medical gases are not included - information from State Agency of Medicines), six enterprises have environmental permits and four of them are also producers of API (see the previous paragraph). Such importers of API own environmental permits such as "LMP" and "PHARMIDEA" (category B permits).

Poland

The main legal act regulating pharmaceutical safety in Poland is the Pharmaceutical Law (06.09.2001 as amended, Journal of Laws of 2020, item 944). The Act specifies i.e.: the rules and procedure for authorizing medicinal products to be marketed, taking into account, in particular, the quality, effectiveness and safety requirements of their use, conditions for the manufacture of medicinal products, conditions for trading in medicinal products, tasks of the Pharmaceutical Inspection and powers of its bodies.

The safety and pharmacovigilance administrative authority responsible for authorizing medicinal products on the market is the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPLWMiPB, www.urpl.gov.pl). The Chief Pharmaceutical Inspectorate (GIF, www.gif.gov.pl) is the authority responsible for the supervision of conditions for the manufacture and import of medicinal products and veterinary medicinal products; the conditions of manufacture, import and distribution of the active substance; the quality and trade of medicinal products, except for veterinary medicinal products.

According to Pharmaceutical Law, only companies entered into the register kept by GIF can deal with the production and sale of medicinal products in Poland. The manufacture of drugs and active ingredients must comply with Good Manufacturing Practice.

The activity of the pharmaceutical industry as a branch of the chemical industry is associated with the possibility of contamination of certain environmental and natural elements. Therefore, environmental permits are required. In Poland, the main legal act regulating these issues is the Environmental Protection Law (27.04.2001 as amended, Journal of Laws of 2020, item 1219). Moreover, in the case of special water use, these issues are included in the Water Law (20.07.2017 as amended, Journal of Laws of 2020, item 310).

Environmental permits can be divided into two categories: integrated permits and sector permits. The integrated permit replaces the sector permits for the following emissions: permit to release gases or dust into the air, permit to generate waste, water permit for water abstraction, a water permit for the discharge of sewage into waters or the ground. A separate permit is a water permit for the introduction of substances particularly harmful to the aquatic environment in industrial sewage into sewage systems. An integrated permit is obligatory for installations using a chemical or biological process to produce pharmaceutical products, including intermediates. According to the Central Statistical Office (GUS) statistics covering companies that employ over nine people, in Poland, about 100 companies are dealing in the production of pharmaceutical substances of various kinds drugs and medical devices. Only twenty-one pharmaceutical companies have an integrated permit (out of the twenty-four installations) and have implemented BAT (data as of 30/09/2019). The remining entities do not produce active substances and therefore, do not use biological processes. As a result, an integrated permit is not obligatory. They only need sector permits for their activities. Two pharmaceutical factories (ZF Polpharma, S.A., Biowet Puławy Sp. z o.o.) have their own sewage treatment plant (as a part of the installation) and they discharge treated sewage into the rivers. However, most factories discharge industrial wastewater into external sewage networks. Therefore, they are required to have a water permit for discharging harmful substances into sewage systems (also those with an integrated permit). The permit should specify the quantity, condition and composition of the introduced wastewater or the minimum percentage of reduction of pollutants in the wastewater treatment process, and – in the case of industrial wastewater – the permissible amounts of pollutants, in particular the amounts of substances particularly harmful to the aquatic environment.

Sweden

The legislation in Sweden concerning the production of API according to consumer safety is harmonised with the legislation in the EU and is essentially the same as in the rest of the EU. The Swedish Medical Products Agency (MPA) is the authority responsible for permission of market pharmaceuticals and supervision of the manufacturing procedures according to consumer safety. Any EC Directives concerning pharmaceuticals are transposed into acts and ordinances by the Swedish Government and into provisions by the MPA. The provisions are published in the MPA's Code of Statutes, LVFS.

The legislation in Sweden concerning any production according to environmental issues such as emissions is the Environmental Code. Production facilities may need a permit according to the Environmental Code to perform production. The need of a permit depends on the type and the size of the production plant and its emissions into the environment.

The Environmental Code is the overall legal basis for any environmental legislation in Sweden and together with different ordinances, it covers provisions for emission into air, water and soil. The Code and its provisions promote sustainable development, and it applies to all activities which could cause negative impacts on human health or the environment. The Code concerns, the management of land and water, nature conservation, protection of flora and fauna, environmentally hazardous activities, water operations, genetic engineering, chemical products and waste management amongst others. Furthermore, the Code sets out the framework for implementing environmental protection through its provisions on procedure, supervision and sanctions. The provisions laid down in ordinances are issued by the Government or in regulations issued by the national authority - the Swedish Environmental Protection Agency (SWEPA). SWEPA also issue general guidelines to assist the interpretation of the Code and underlying legislation.

The provisions of the Environmental Code provide a basic framework and do not entail specifics, such as emission limits. However, an important feature of the Code concerning emission limits is the permit procedure, particularly the conditions concerning the use of a permit. In principle, the permit stipulates the conditions under which an activity may be carried out and the production of a certain quantity of an API is permissible subject to certain conditions. The conditions are set out for each activity connected to the current circumstances such as the technology and processes applied, as well as the environment around each plant. Hence the conditions may vary between two plants of API production.

The Permit authorities are the Land and Environment Courts and the Environmental Permitting Committees (EPC), the latter being a special branch of the County Administrative Board (CAB). In general, the division of competences for permitting is based on the activity concerned, its typical environmental impact and the significance of the impact.

To oversee compliance with the requirements set out in the Code, legislation issued under the Code, as well as the requirements set out in permits, the Code contains provisions concerning supervision, i.e. inspection and enforcement. The supervision of compliance according to environmental permits is carried out at the regional or local level by the CABs or local Environmental and Public Health Committees. The SWEPA is responsible for issuing guidelines concerning supervision to those responsible for operative supervision.

However, the operators of environmentally hazardous activities for which a permit is required also have a responsibility to minimise and control the environmental impact of their activities by a system of compliance based on self-monitoring by operators. The operator must continuously monitor the operation of the activity to mitigate or prevent detrimental impacts on human health or the environment as well as submit an annual environmental report to the supervisory authorities.

An environmental permit is an authorization issued by the Environmental Board, which grants the developer the right to use natural resources (e.g. water, minerals, etc.), to generate pollutants (e.g. waste gases) and waste. There are various environmental permits: integrated environmental permit, ambient air pollution permit, a special permit for use of water, waste permit, permit for general geological research, permit for geological exploration, permit for extraction of mineral resources, and permit for radiation.

3.2. Application of requirement for use of best available techniques

For all IED companies BAT techniques are obligatory. The BAT techniques are defined by the EU commission in the BREF-documents. The company can check which of the 28 sectors/activities they are categorised under, and thereby have knowledge of which BAT technologies they are expected to use. The same can be found for all sub activities, conclusions set forward by the 2010/75/EU

If the company cannot be categorized according to the 28 sectors/activities, certain criteria in the Declaration of Approval has to be used in the presentation of BAT.

For smaller companies (Category 2, non-IED facilities), the authority will then determine if the applied techniques are sufficient to minimise the emissions.

Upon determination of the integrated permit requirements based on such BAT, which are not described in any applicable BAT conclusions or which are determined for the activities or processes concerned, the issuer of permits shall be guided by the following criteria:

1. the use of low-waste technology;
2. the use of less hazardous substances;
3. the recovery and recycling of substances generated in production, and of waste;
4. the use of comparable processes, facilities or methods of operations which have been tried with success in manufacture on an industrial scale;
5. technological advances and the results of scientific development;
6. the nature, impacts and volume of the emissions concerned;
7. the commencement date of the activity of the installation;
8. the length of time needed to introduce the best available techniques;
9. the consumption and nature of raw materials used, including water, and their energy efficiency;
10. the impact of the emissions on the environment and prevention of the risks resulting therefrom or reduction thereof to the maximum extent possible;
11. prevention of accidents and minimisation of the consequences thereof;
12. relevant information published by international organisations concerning the best available techniques

3.3. The validity of the permit

An environmental permit is generally given without an expiration date. A temporary environmental permit can have varying length.

In Estonia, integrated environmental permits are issued without a time limit, but the requirements could be converted if:

- the provisions provided by legislation on which the requirements of the permit are based do change;
- the contamination is of such significance that adverse changes are caused to the site of the installation, wherefore the existing emission limit values need to be reduced or additional limit values need to be determined;

- changes in the best available techniques make it possible to substantially reduce emissions or the hazard created thereby without imposing excessive costs;
- to prevent accidents, techniques different from those determined by the integrated permit are required;
- substantial changes in the nature or functioning of the installation have been imposed or are proposed.

In Finland, environmental permits for industrial plants valid for the time being may be voided (activities according to YSL 88 §), if

- activities have stopped for a minimum time of five years;
- if the activity operator notifies that operations have stopped or that they will not be started;
- activities have not started within five years (or other time frame set in the permit) of issuing the permit;
- the environmental permit was not reviewed appropriately, when new conclusions concerning the IED-facility have been published by the European Commission.

In Germany, operating permits according to BImSchG and 4th BImSchV are issued without a time limit, but the requirements can be changed if:

- the construction or operation of the installation has not commenced within a reasonable period set by the approval authority or
- an installation has not been operated for a period of more than three years;
- changes in the best available techniques make it possible to substantially reduce emissions or the hazard created thereby without imposing excessive costs;
- the provisions provided by legislation on which the requirements of the permit are based are changed;
- substantial changes in the nature or functioning of the installation have been imposed or are proposed.

In Latvia, a regional environmental board shall, per the procedures prescribed by the Cabinet, review permit conditions and, if necessary, renew or supplement them in the following cases:

- when information regarding the negative effects of pollution on human health or the environment have been received, the limit values of environmental quality requirements have been exceeded, or amendments to the laws and regulations determining the environmental quality requirements have been made;
- the European Commission has issued new conclusions regarding the best available techniques for the polluting activities (installations) indicated in Annex 1 to Law On Pollution;
- when following an opinion of State institutions, the use of another technology is required to guarantee the safety of the process;
- to ensure the issuance of the permit under the conditions referred to in Section 31, Paragraph seven of Law On Pollution (requirements for the energy efficiency in relation to conditions of the greenhouse gas permit);
- when it is determined by other laws and regulations;

- before changes to the polluting activity;
- if it is provided for in the conditions of the permit;
- in the cases specified in Sections 50 and 51 of Law On Pollution (procedures for dispute of decisions, examination of submissions);
- if the pollution created by the installation is substantial in that it is necessary to review the conditions of the permit or the emission limits specified therein or to specify new emission limits in the permit.

In Poland, an environmental permit is issued for a specified period of time, not longer than ten years, except for an integrated permit which is issued for an indefinite period. At the request of the operator of the installation, the integrated permit may be issued for a specified period. Moreover, a water permit for the discharge of industrial wastewater containing substances particularly harmful to the aquatic environment is issued for a period not longer than four years.

The environmental permit expires:

- after the expiry of the period for which it was issued;
- if the entity has ceased to be an installation operator within the meaning of the Environmental Protection Law, or for other reasons, the permit has become redundant;
- at the request of the operator of the installation;
- if the operator of the installation has not commenced the activities covered by the permit within two years from the date on which the permit became final;
- if the operator of the installation has not conducted the activity covered by the permit for two years.

The authority competent to issue the permit also analyses the integrated permit:

- at least every 5 years or
- if the environmental impact of the installation has changed to the extent that it is necessary to change the permit in the part related to the conditions or emission levels specified therein, or
- if there has been a change in the best available techniques, allowing for a significant reduction in emissions without causing excessive costs, or it results from the need to adapt the operation of the installation to changes in environmental protection regulations.

In Sweden, the environmental permits are issued without a time limit, but the requirements could be changed if:

- the provisions provided by legislation on which the requirements of the permit are based are changed;
- the contamination is of such significance that adverse changes are caused to the site of the installation, wherefore the existing emission limit values need to be reduced or additional limit values need to be determined;
- changes in the best available techniques make it possible to substantially reduce emissions or the hazard created thereby without imposing excessive costs;
- to prevent accidents, techniques different from those determined by the integrated permit are required;

- substantial changes in the nature or functioning of the installation have been imposed or are proposed.

3.4. Monitoring and supervision

The monitoring program is an important and required part of permits in EU countries. The authority, whether it is the municipality or an environmental protection agency, must perform active and investigative supervision of the companies. They must supervise the rules according to the environmental protection law and supervise that all injunctions and prohibitions are within compliance.

The supervision program is based on guidance and preventions rather than control. The companies are invited to a dialog with the authorities where possibilities of alterations to the process and production are discussed before a violation occurs.

Self-monitoring is to be determined based on the requirements for self-monitoring contained in the applicable BAT conclusions and environmental permits.

Emission limit values for the following substances are mostly determined in EU countries, concerning emissions into water:

- organohalogen compounds and substances which may form such compounds in the aquatic environment;
- organophosphorus compounds;
- organotin compounds;
- substances and mixtures with carcinogenic or mutagenic properties or properties which may affect reproduction in or via the aquatic environment;
- persistent hydrocarbons and persistent and bioaccumulable organic toxic substances;
- cyanides;
- metals and their compounds;
- arsenic and its compounds;
- biocides and plant protection products;
- suspended solids;
- substances which contribute to eutrophication, including in particular, nitrates and phosphates;
- substances which have an adverse impact on the oxygen balance and can be measured using parameters such as biological oxygen demand (BOD), chemical oxygen demand (COD) or other similar parameters;
- priority substances and priority hazardous substances established on the basis of the EQS Directive 2013/39/EU

There are no water quality standards or emission limit values /criteria set on wastewater APIs from pharmaceutical plants and recipient surface water in the Baltic Sea region. It is important to monitor APIs produced in the pharmaceutical plant, but also chemicals used in the technological process discharging waste water into the environment. Environmental permits must be granted taking into account the necessary requirements for estimating APIs emissions from pharmaceutical plants.

3.5. Overarching permit conditions concerning waste water treatment

Water quality limits are set mostly for effluents that lead into the environment. These quality limits are determined by the capacity of wastewater treatment plants and include nutrients and hazardous substances. Active pharmaceutical ingredients (APIs) are not included in regulations, although they can have properties that affect the environment.

In Estonia there is a contradiction between the requirements of law and an application of integrated environmental permits:

- The industrial Emissions Act (§44) states that the emission limit values and equivalent parameters or technical measures that are provided for integrated permits are based on BAT. The emission limit values shall apply at the point where emissions leave the installation. Any dispersion or dilution of emissions by other substances or environmental media before discharging into the environment shall be disregarded when determining emission limit values. Concerning indirect releases into the water the impact of a water treatment plant may be taken into consideration when determining the emission limit values of the installation involved, provided that an equivalent level of protection for the environment is guaranteed, contamination is not increased and the operator complies with the requirements established concerning hazardous substances discharged into the public sewerage system [3];
- The industrial Emissions (§19, subsection 2.15) Act also states that an integrated permit is required for the independently operated treatment of wastewater discharged from installations operating in the areas of activity specified in clauses 1) to 14) of this subsection, except for the treatment of wastewater in the water treatment plants of a public sewerage system [3]. The limit values for effluents are set with Regulation No. 99 [32]. As a rule, indirect discharges are not permitted in Estonia.

In Finland according to Finnish legislation (YSL 67 §, YSA 41 §) industrial waste water must be properly pretreated when leading it to a municipal waste water treatment plant. This requirement aims at ensuring that i.e. harmful effects are avoided in the waters receiving the MWWTP effluents, and, that safe and acceptable utilisation of wastewater sludge is not jeopardised. If the requirements are not met, MWWTP is free to decline to receive the industrial waste water (YSA 41 §).

Some overarching permit conditions, broadly aimed at minimising the environmental impact of permitted activities, identified in Finnish environmental permits issued to the pharmaceutical industry [30] are:

- Permitted activities must be run in a way that minimises their environmental impacts;
- Permit holders must be aware of the concentrations of harmful substances in waters leading from their facility and into either municipal wastewater networks or stormwater drainage networks as well as their impacts in WWTPs and ditches;
- The facility must see that wastewater emissions do not cause harm to the performance of the receiving WWTP;
- Wastewater leading to the sewer network must not cause harm or danger to the network, properties along the network or pumping stations;
- Wastewater leading to the sewer network must not complicate sewage sludge processing or utilisation;

- The facility must have a permit/agreement with the municipal water company for leading wastewaters into the municipal sewer network;
- If there are unintended emissions in the facility grounds, wastes and spillages containing harmful substances must be collected and delivered to appropriate treatment facilities;
- The recipient WWTP must be notified if the contents or quantities of waste waters differ from normal, or if substances potentially harmful to WWTP processes have been emitted into the sewer network;
- Wastewater must not be diluted;
- Wastewaters generated from the washing of facility instruments, which contain harmful substances must delivered to hazardous waste treatment facilities;
- Wastes, hazardous or otherwise, must not be flushed into the sewer;
- The wastewater load to the WWTP is to be decreased through process technology or pretreatment;
- Liquid chemicals and chemical wastes are to be stored so that possible spillages can be limited;
- Firefighting water collection must be designed so that waters containing chemicals, or that could cause harm to the environment do not enter the environment, groundwaters or sewer networks;
- Permit holders must be sufficiently aware of developments in the best available technology in the field and must prepare for implementing those technologies.

In **Germany,** the discharge of waste water is regulated in the Water Resources Act (WHG) and the Waste Water Ordinance (AbwV). Within the WHG two options for the discharge of waste water are defined:

- direct discharge (discharge into the environment): The legal requirements for the discharge of wastewater is regulated in §57 of the Water Resources Act (WHG). Wastewater must be treated according to the Best Available Techniques (BAT). The requirements for industrial wastewaters are specified in the annexes of the Waste Water Ordinance (AbwV). For the chemical industry the annex 22 of AbwV is obligatory.
- Indirect discharge (discharge into the sewage system): According to § 58 WHG, approval must be given by the local authorities for the discharge of waste water into public sewage systems (indirect discharge). For companies that are assigned to the Waste Water Ordinance (AbwV) (e.g. chemical industry) whose wastewater is polluted with harmful substances, which are hardly eliminated in WWTPs, must pretreat their wastewater according to BAT criteria. Therefore, the requirements for direct discharge are obligatory.

In Latvia, the discharge of untreated waste water into the environment or surface water is prohibited.

A requirement is set in environmental permits for operators to conclude an agreement with owners of centralised wastewater collecting systems for three manufacturers of APIs with environmental permits, that do not have their wastewater treatment plants: “NORTHERN SYNTHESIS”, “Grindeks”, “RĪGAS FARMACEITISKĀ FABRIKA”.

Monitoring results and quality requirements for wastewater from these agreements with owners of centralised wastewater collecting systems are not publicly available.

It is prohibited to discharge hazardous chemical residues and waste into the sewage system by dissolving them.

There are different requirements for pretreatment of wastewater for manufacturers of API:

- Solid separation / settling tank; a separate collection of effluent from the production; basic wastewater from production is acidified before being discharged into the industrial sewerage system; all industrial wastewater is pretreated in biological WWTP;
- Grid trap; activated sludge; industrial acid wastewater is neutralised with alkali before discharging into an industrial sewage system;
- Mechanical wastewater treatment facilities;
- In one case, in an environmental permit, it was concluded that so far the company's wastewater management and control has not been carried out per the recommendations of Best Available Techniques Reference Documents as production wastewater (liquid hazardous waste) is diluted in a large tank and gradually discharged into the sewer to reduce the concentrations of hazardous substances to the norms of the chemical oxygen demand specified in the contract with the wastewater treatment plant.

Quality standards are defined for such parameters as oil hydrocarbons, suspended solids, chemical oxygen demand; all parameters from chapter 4; chloroorganic compounds (AOX) (one case).

There are overall requirements for the management of wastewater for importers of API: prohibiting the discharge of untreated wastewater into the environment and hazardous chemical residues and waste into sewage systems by dissolving them, and the requirement for the conclusion of the agreement with the owner or manager of the centralised sewerage system or treatment plant. There are no requirements for the monitoring of wastewater for these importers of API in environmental permits.

In **Poland**, the conditions that must be met when discharging industrial wastewater into waterbodies or the sewage system are regulated by two legal acts. The first is the Water Law Act (mainly Articles 99 and 100) along with executive regulations (Journal of Laws of 2019, items 1220, 1300 and 1311). The second is the ordinance of the Minister of Construction on the manner of fulfilling the obligations of industrial wastewater suppliers and the conditions for discharging wastewater into sewage devices (Journal of Laws of 2016, item 1757).

The supplier of industrial wastewater by introducing it to sewage devices ensures:

- elimination or limitation of substances particularly harmful to the aquatic environment, specified in the regulation (Journal of Laws of 2019, item 1311);
- even discharge, according to the throughput of the channels and the permissible load of the WWTP;
- reduction of those pollutants that adversely affect the operation of WWTP .

Industrial wastewater must be pretreated before discharging into the sewage system, it and may not exceed the permissible values of indicators for substances particularly harmful to the aquatic environment (e.g. Hg, Cd) and other polluting components (e.g. BOD_5, COD, total N, total P, volatile phenols, BTX, chlorides). Moreover, sewage must not be diluted to obtain permissible index values. The installation of the necessary industrial wastewater treatment devices should be performed in accordance with the best available techniques, in particular, the reduction of the impact of sewage on the environment.

Industrial wastewater may be discharged into sewage systems if:

- it does not pose a threat to the safety and health of people operating sewage systems, the condition of the structure construction and proper operation of these devices and sewage treatment plants, as well as to meet the water and sewage conditions (for companies) set out in the water permit for discharging sewage into water or soil and the use of sewage sludge;
- the industrial sewage supplier meets the conditions of the water permit if such a permit is required under the provisions of the Water Law;
- the temperature of this sewage does not exceed 35° C, and the pH value is in the range of 6.5 to 9.5, exceptfor wastewater containing cyanides and sulphides with a pH of 8 to 10;
- are susceptible to mechanical and biological treatment processes.

In Sweden, several laws and regulations sets quality standards and limits to what a plant can release into the public wastewater systems, and this also includes plants that produce APIs. The legislation is a combination of EU-regulations and directives as well as legislations issued by the Swedish environmental government. The quality limits are also determined by the capacity of the municipal wastewater plants and its environmental permit including the release of nutrients and hazardous substances permits.

3.6. Permit conditions concerning API emissions – Good Practices

As a rule the environmental permits in studied countries very rarely contain any permit conditions regarding APIs. The permits do not state specific concentrations of the different contaminants. There are no overarching conditions in the permits that are aimed at decreasing API emissions and their impacts (i.e. influence to the sewage sludge etc.).

The environmental assessment which must always be carried out, will contain information regarding the concentration limits of different substances. The most normal case is that the industry is regulated after the normal wastewater parameters such as BOD, COD, N, P and suspended solids. The authorities have the possibility of introducing restrictions on hazardous substances such as PAHs, metals or other groups of substances. Due to the complexity of measuring APIs, there are generally no industrial regulations that contain APIs.

In Finland only a few environmental permits contain explicit conditions concerning API emissions. However, the three most recently issued permits from the years 2013–2016 give specific requirements concerning the estimation or reduction of pharmaceutical emissions. Äystö et al. (2019) studied altogether 13 plants posing an environmental permit. Two permits had obligations to measure pharmaceutical concentrations in wastewater, and one permit had obligations to measure ecotoxicity of wastewater.

Permit conditions given in Finnish environmental permits issued to the pharmaceutical industry include e.g. the following conditions:

- Wastewaters containing significant amounts of non-biodegradable pharmaceuticals or their intermediates, generated in industrial processes, must be treated with necessary methods

so that the concentrations in WWTP effluent wastewaters are decreased to a level that can be assumed not to cause harm to the environment;
- The operator must carry out measures to reduce the pharmaceutical load entering the sewer network;
- Unsalable products are waste. Wastes are not to be flushed into the sewer;
- Pharmaceutical residues and toxicity of waste waters directed from the facility to the WWTP must be screened once when producing different pharmaceuticals and intermediates. The research plan must be delivered to the supervising authority one month before carrying out the research;
- Pharmaceutical concentrations in the waste waters directed to the sewer must be analysed once annually.

The Finnish study by Äystö et al. [30] proposed good practices and recommendations on industrial pharmaceutical emissions and how they could be further reduced. In general, improving the estimates of pharmaceutical emissions and promoting the setting of limit values for pharmaceutical residues and bioassays on wastewaters originating from the pharmaceutical industry were considered especially necessary and important [30]. Similar and harmonised plant-specific API risk assessments are recommended. The good practices and recommendations were grouped into three categories with some examples:

- Pharmaceutical plants must be aware of their API emissions and impacts on MWWTPs and surface waters
    - Emissions should be estimated in a calculative way (recommended) or via measuring, or with their combination on those APIs handled in the plant
    - The permit holder must estimate the significance of API emissions when performing risk assessment at plant level in cooperation with supervisory authorities
        - cover the MWWTP and recipient water
        - if risks are found, necessary measures to decrease these risks must be presented
    - It is recommended that the, industrial waste waters discharged to the MWWTP to be tested with bioassays (inhibition of nitrification) to ensure efficient functioning of the MWWTP
- Recommendation on limit values for APIs & bioassays
    - Whenever inhibition of nitrification is detected, the cause needs to be identified
    - Limit values for pharmaceutical concentrations should be based on plant-specific considerations
    - When setting limit values, it is important to ensure collaboration between authorities, water companies and the industry operator
- Good practices for the management of wastewater and waste from the pharmaceutical industry
    - Wastewater and waste fractions containing significant amounts of pharmaceuticals are to be collected separately and to be delivered to special hazardous waste treatment
    - Unsalable products (e.g. failed medicine batches) are waste and are not to be discharged into the sewer

4. Industrial wastewater contracts between pharmaceutical plants and municipal wastewater treatment plants

The main route by which pharmaceuticals reach the aquatic environment is via effluents from sewage treatment plants receiving wastewater from households and hospitals [10].

The industrial wastewater discharge into municipal wastewater systems is a subject of international, national and regional legislation [10]. On the EU level, directive concerning urban wastewater treatment (UWWTD, 91/271/EEC) states in Article 11 and Annex I that all EU Member States must ensure that discharge of industrial wastewater into collecting systems and urban wastewater treatment plant is subject to prior regulations and/or specific authorisations by the competent authority or appropriate body" and the "industrial wastewater entering collecting systems and urban wastewater treatment plants shall be subject to pretreatment".

According to the 91/27/EEC [10] industrial wastewater must fulfil the following requirements, if it is related to the municipal wastewater collection system:

- protect the health of staff working in collecting systems and treatment plants;
- ensure that collecting systems, wastewater treatment plants and associated equipment are not damaged;
- ensure that the operation of the wastewater treatment plant and the treatment of sludge is not impeded;
- ensure that discharges from the treatment plants do not adversely affect the environment, or prevent receiving water from complying with other Community Directives;
- ensure that sludge can be disposed of safely in an environmentally acceptable manner.

Although there are no specific requirements for quality of industrial wastewater presented in the 91/271/EEC, HELCOM recommends (28E/5, [33]) to set limit values for substances harmful to the receiving waters which cannot be treated in the municipal wastewater treatment plants or which are harmful to the sewerage systems or the processes of the treatment plant and these substances should be therefore established separately for industry and other relevant sectors discharging indirectly based on the BAT and BREF [5]. Annex I in 91/271/EEC [10] as well as HELCOM recommendation 28E/5 [33] both set an obligation for BSR countries to establish regulations for wastewaters discharged to the public sewer system. As a result, all BSR countries have set some (basic) rules to avoid disturbances in the municipal wastewater treatment plants.

As a rule, the pharmaceutical industry has to have an environmental permit to run the facility (except in Russia, which is at the beginning of the process of implementing the integrated permitting system, and in Estonia, where there have been no environmental permits issued for the pharmaceutical production facilities). The pharmaceutical industry must get an initial approval to discharge industrial wastewaters into the public sewer system from the authorities and water utilities. The industrial wastewater contract and environmental permit are separate documents and independent of each other. However, a contract is usually needed for such an industry that falls under the environmental permit obligation and the need for a contract may be included within the terms of an environmental permit. It is also possible to draw up a contract with an industry that does not hold an environmental permit.

Industrial wastewater contracts are required if the wastewater conveyed to a public sewer diverges in terms of amount or quality from domestic wastewater so, that it may affect operations of water utility (e.g. work safety, condition of network, treatment process, quality of sludge). Contracts might also be needed if the wastewater contains substances that may affect the state of the receiving waterbodies (e.g. in Finland). During an environmental assessment, which is carried out as a part of integrated permitting, the capacity of the receiving wastewater treatment plant is also taken into account while setting quality standards for the industry. All changes in the wastewater flow, which are not within the permit, must be reported beforehand to both the public wastewater treatment plant and to the relevant authorities, which will then assess the changes. If permanent changes are to be made, a new environmental assessment must be carried out. No other cooperation is mandatory for the industrial partner, as long as all discharge limits are over held. Also there are some good cooperation examples to be found from BSR countries (e.g. Finland), the overall knowledge of industrial wastewater characteristics, treatment technologies and impact on municipal wastewater systems, that both industrial organisations and water utilities have, has proven to be insufficient according to the findings from the BEST project [17]

Industrial wastewater contracts are not public documents and therefore there is no complete information about their content. Also, the legislation does not set specific requirements for their content, but there are some national guidelines available [34].

In **Denmark** there are no pharmaceutical plants that hold a separate discharge permit. The wastewater is discharged into the public sewer system and treated at the public wastewater treatment plant. The pharmaceutical plants are obliged to do a separate analysis of their discharge flows, to follow the concentrations of the waste water. Pretreatment is necessary if the wastewater cannot meet the requirements for discharge.

The pharmaceutical industry must get initial approval to discharge its wastewater into the public sewer system. When the environmental assessment is carried out, the capacity of the wastewater treatment plant, which will receive the wastewater, is also considered. All changes in the wastewater flow, which are not within the permit, have to be reported beforehand to both the public wastewater treatment plant and to the relevant authorities, who will then assess the changes. If permanent changes must be made, a new environmental assessment must be carried out. No other cooperation is mandatory for the industrial partner, as long as all discharge limits are overheld. Cooperation and communication between the industry and the public wastewater treatment plant are widely practiced, although the industrial partner is often a significant part of the wastewater flow.

All discharge limits are based on common wastewater parameters such as COD, suspended solids, total nitrogen and total phosphorous.

In **Estonia,** practically all industrial plants that do have an integrated permit and lead their wastewater to the public sewer system must have a contract with the water company owning the wastewater treatment plant. The contract and additional materials required by the Ministry of Environment regulation No. 18 [35] paragraphs 5-7 must be presented to the Environmental Board. Usually the data presented to the Environmental Board is not published in the integrated permit, only replaced by the following: *"Data is not provided because it is not relevant in this context."*

All pharmaceutical plants are leading their wastewater to the public sewer system. According to the feedback received from three water companies that are collecting and treating wastewater from pharmaceutical plants, the following can be concluded:

- All pharmaceutical plants do not have any special quality standards for wastewater quality;
- All contracts are based on regulations for domestic wastewater and nutrients (BOD_7, COD, N, P and TSS), hydrocarbons (C_{10}–C_{40}) and pH are to be monitored according to these regulations. So far, the wastewater from the pharmaceutical plants has not been analysed;
- Contracts do not set any obligations for pretreating the wastewater from pharmaceutical plants. Water companies do not have any information about the existence of pretreating facilities in these pharmaceutical plants.

In **Finland,** the parties involved and related to industrial wastewater contracts of pharmaceutical plants are municipalities, water utilities, Regional State Administrative Agencies (AVIs) and Centers of Economic Development, Transport and the Environment (ELY). The operator, in this case – a pharmaceutical plant, negotiates an industrial wastewater contract with the water utility, which has an operational area approved by the municipality.

Industrial wastewater contract and environmental permits are separate documents and independent of each other. However, a contract is usually concluded with such an operator who falls under the environmental permit obligation and the need for a contract may be included in terms of environmental permit. Case-specifically the contract is also possible to conclude with an operator that does not hold an environmental permit.

Industrial wastewater contracts are needed if the wastewater conveyed to public sewers diverges in terms of amount or quality from domestic wastewater so, that it may affect operations of water utility (work safety, condition of network, treatment process, quality of sludge). Contracts are also needed if wastewater contains substances that may affect the state of the receiving waterbody.

Industrial wastewater contracts are not public documents, and therefore there is no complete information about their content. Also, the legislation does not set specific requirements for their content. The Finnish Water Utilities Association has recommended, that it should be considered on a case-by-case basis if industrial wastewater contracts made with the pharmaceutical industry should require the industrial operator to monitor pharmaceutical emissions from the plant [34].

Based on three industrial wastewater contracts received from water utilities, industrial wastewater contracts concerning pharmaceutical plants do not set boundaries for APIs in wastewater discharged to WWTPs. Water utilities can order that rinse waters containing APIs which are formed during pharmaceutical production must be collected to a container and delivered separately to the treatment instead of conducting to the sewer network.

In **Germany,** not much is known about pharmaceutical installations that hold a separate discharge permit. Normally the wastewater is discharged into the municipal wastewater system. Contracts for the indirect discharge of wastewater are based on regulations for domestic wastewater and nutrients (BOD7, COD, N, P and total suspended solids), hydrocarbons (C10–C40) and pH. The analysis is supposed to be carried out by external, credited laboratories or specialised persons from the municipal WWTP. Pretreatment is necessary if the wastewater cannot meet the requirements for discharge

In **Latvia,** according to publicly available information, there are requirements for monitoring parameters with owners of centralised wastewater collecting system (“Rīgas ūdens” in Latvian case) according to 15.12.2017 Riga City Council Binding Regulations Nr. 17 “Binding regulations of

operation, use and protection of Riga city centralised water supply and sewerage system. There is a set maximum allowable concentration for parameters such as suspended solids, chemical oxygen demand, total nitrogen, total phosphorus, extractable substances, oil products, synthetic surfactants, total chromium, nickel, zinc, copper, arsenic, lead, mercury, phenol index, formaldehyde, cadmium.

In **Poland**, most pharmaceutical plants discharge industrial wastewater into the public sewage system and they are treated at the municipal WWTP. Therefore, plants need a contract with a water sewage company for the discharge of industrial wastewater into the sewage system (according to the Act on collective water supply and collective sewage disposal (07.06.2001 as amended, Journal of Laws of 2019, item 1437)). The contract specifies in detail the type of discharged wastewater. It takes into account the parameters of wastewater, determined based on the Regulation of the Minister of Construction (Journal of Laws 2016, item 1757) on the manner of fulfilling the obligations of industrial wastewater suppliers and the conditions for discharging wastewater into sewage systems. Contracts are not publicly available.

The values of the contamination indicators should be met in the daily flow-proportional average sample mixed with manually or automatically taken samples at intervals of at least two hours. For reaction and temperature, the values refer to single-use samples taken at random. The collection of control samples of industrial wastewater introduced to sewage devices should be performed by the suppliers of this wastewater from representative places, i.e. allowing the assessment of the total amount of pollutants in the industrial wastewater from the entire plant.

In **Sweden,** all pharmaceutical plants discharge their wastewater into the public sewer system and it is treated at the public WWTP. However, the plants do not have separate contracts with WWTP.

When an environmental assessment which meets the requirements in the permits is carried out, both location and production capacity are considered as well as the capacity of the WWTP and status of the environment. However, some similarities in the permits can be noted. Requirements in the permits are often based on regulations for domestic wastewater and nutrients (BOD, COD, N, P and TSS) and pH. The pharmaceutical plants might also be obliged to do separate analyses of their discharge flows and focus on the concentration of a specific substance.

Issues identified

1. Most of the pharmaceutical plants in the BSR have integrated environmental permits (except in Estonia and in Russia) that also set conditions for indirect discharges. Estonian partners have contacted Environmental Inspectorate regarding the issue. Russia is implementing the new system for environmental permitting and it is still too early to analyse its outcome.
2. All EU countries have implemented regulations for effluent quality per 91/271/EEC, 2010/75/EU, 2008/105/EC and 2013/39/EU, but these do not contain APIs. There are no national or regional quality standards/emission limits for APIs in wastewater. The discharge permits are generally built around the normal wastewater characterisations for nutrients (COD, TN, TP SS, pH) and monitored accordingly. There are possibilities of regulating other parameters, such as heavy metals (e.g. Hg, Pb, Cd) or organic substances (e.g. PAH, DEHP, oil/grease in Denmark or phenols, formaldehyde, synthetic surfactants in Latvia) or some other substances (e.g. salts in Denmark - Na, Cl), but these are based on regional or municipal regulations and vary according to the competency of the regulating party and/or water utility. Based on the information received from water utilities, industrial wastewater contracts

concerning pharmaceutical plants do not set quality standards for APIs in wastewater discharged to municipal WWTPs.

3. There is a huge gap in information available about *in situ* pretreatments of pharmaceutical wastewater. As a rule, contracts do not set any obligations for pretreating the wastewater from pharmaceutical plants (except in Germany and in Denmark, where pretreatment is considered necessary if the wastewaters cannot meet the requirements for discharge). Most water utilities do not have information about the existence of pretreating facilities in pharmaceutical plants.
4. Despite a universal recommendation by HELCOM (28E/5), it was reported only by Finland that water utilities can order rinse waters containing APIs, which are formed during pharmaceutical production, to be collected to a container and delivered separately to the treatment instead of discharging into the sewer network.
5. Wastewater from hospitals contain high levels of certain APIs, but hospitals are not (and should not be) considered to be production units. Still, hospitals can be considered to be relevant point sources in the sewage catchment area and therefore they might need similar contracts to minimise negative environmental impacts and potential issues in receiving MWWTP. This has also been recommended in the Finnish Industrial Wastewater Guide [34].
6. The consumption of certain pharmaceuticals may be concentrated on hospital premises. For instance, in Finland, over 90 % of the sales for many systemic antibacterial agents are covered by hospitals [36]. The pharmaceutical concentrations detected in hospital wastewaters often exceed those in WWTP influents [e.g. 37, 38, 36]. Hospitals may also account for a significant portion of the total load of specific APIs to the recipient WWTP. For instance, Ort et al. [37] identified a hospital to account for over 15% of the antibiotics roxitrhomycin and trimethoprim in the influent of the receiving WWTP. Similarly Sörengård et al. [39] identified a hospital to account for all of the clindamycin and metronidazole loads received at the receiving WWTP. On the other hand, Santos et al. [40] reported hospitals to account for 49% of analgesic loads and 13% of the load of contrast media. However, it has also been concluded that compared to the quantities emitted from the rest of the society (households etc.), loads originating from hospitals are generally low except for a limited number of APIs [41]. Nevertheless, when estimating the importance of hospitals as point sources, the specific activities within the hospital and usage patterns of the relevant APIs must be carefully considered e.g. contrast media are likely administered mainly in hospital premises, but if the patients do not stay in the hospital, these substances may be excreted outside the hospital.

5. Conclusions and recommendations

Conclusions

The manufacturing of pharmaceutical products can be defined as the chemical synthesis, fermentation, extraction, formulation and finishing of pharmaceutical products and, where carried out at the same site, the manufacture of intermediate products.

In EU countries the most relevant regulations regarding the aim of reducing emissions of APIs to the water environment are the Industrial Emissions Directive, Water Framework Directive, and Urban Waste Water Treatment Directive.

The pharmaceutical industry is a major industrial asset to the European economy, strongly research-based and one of the best performing high technology sectors. The total number of pharmaceutical plants that produce APIs within the Baltic Sea catchment area has been difficult to estimate.

There were:

- 82 facilities listed in E-PRTR database with activities within NACE code C21 - Manufacture of basic pharmaceutical products and pharmaceutical preparations in 2017 ;
- 647 companies with Manufacturing and Importation Authorisation (MIA);
- 2468 companies that hold a Good Manufacturing Practice (GMP) within the Baltic Sea catchment area.

More facilities are situated in Denmark and Sweden, and Poland according to the MIA database and E-PRTR database, respectively.

In EU BSR countries permitting of the pharmaceutical industry can be divided into two general categories – integrated permits and other permits (single-medium permits). All countries use integrated permits for pharmaceutical plants that are subject to IED. While other permits could be given out to control certain emission individually (or with a narrow scope), an integrated permit is required for the operation of the installation as a whole.

In the Russian Federation, federal legislation sets out the fundamentals of regulation in the sphere of health care. Production of pharmaceuticals may be carried out by manufacturers that have a license for the production of pharmaceuticals. Integrated environmental permits are issued to legal entities and sole traders operating category I environmentally hazardous facilities.

For all IED plants, BAT techniques are obligatory. The BAT techniques are defined by the EU commission in the industrial sector specific BREF-documents.

The self monitoring program is an important part of an environmental permit. Emission limits for some specific parameters are set only for effluent which is led into the environment. These emission limits are determined by the capacity of the wastewater treatment plant and include nutrients and some hazardous substances. APIs have not been included in permits' monitoring programs and no emission limits are set for them.

Most of pharmaceutical plants discharge their wastewater into the public sewer system. The pharmaceutical industry has to get approval to discharge its wastewater to the public sewer system and must have an industrial wastewater contract or agreement with the appropriate water company. These contracts are not public.

Recommendations

- Pharmaceutical plants should be aware of their API emissions and impacts on MWWTPs and surface waters. Emissions should be estimated in a calculative way or via measuring or combining those APIs handled in the plant.
    - It is important to monitor those APIs produced (and included) in pharmaceutical products, and the chemicals used in the technological process, that are discharged into the environment. Environmental permits must set the requirements for estimating emissions of APIs from pharmaceutical plants.
    - It is recommended to establish water quality standards in the effluents for those APIs involved in manufacturing of pharmaceuticals in the pharmaceutical plant.
- The wastewaters leading to the sewer network must not cause harm or danger to the municipal sewer system, network properties, or pumping stations; they should not complicate sewage sludge processing or utilisation. Although there are usually no quality standards or emission limit values for APIs, performing routine inhibition tests at the plant to prevent disturbances in MWWTPs is recommended.
- The pharmaceutical plants are obliged to conduct a separate analysis of their discharge flows, following the wastewater's API concentrations. They are to inform the WWTP operators about any changes. Cooperation and communication between the industry and the public wastewater treatment plant are to be improved.
- Control system for the pharmaceutical industry involving environmental permits and industrial wastewater contracts, should be enforced in all BSR countries. To discharge industrial wastewater into the public sewer system, the pharmaceutical plant must first get approval from the authorities and the water utility. Although there is a possibility to make a contract with the industrial facility that does not have an environmental permit, the permit itself ensures better control over actions taken by the industrial facility. It also helps enforce the implementation of BAT.
- If the quality of waste water cannot meet the requirements for discharging into municipal sewer, then it is necessary and recommended to perform pretreatment. Under IED, all pharmaceutical production plants operating at the industrial level should uphold conditions set in relevant BAT documents for the chemical industry to minimise pharmaceutical emissions.
- Hospitals should have contracts with waste water treatment plants like industrial wastewater contracts.
- Wastewater from the pharmaceutical industry as well as from hospitals contains a wide variety of APIs. It is not feasible to monitor all the API substances in these waters. In addition to some specific APIs selected based on plant specific risk assessment, monitoring programs could contain domestic waste water parameters (COD, BOD, TN, TP SS, pH), and heavy metals, BTEX, PAH and VOC should also be included [34]. If necessary, nitrification and/or denitrification inhibition should be tested to examine the impact of the industrial (or hospital) wastewater on the nitrogen removal bacteria (i.e. functioning of MWWTP). Regular testing of inhibition should be required especially from pharmaceutical industry

facilities whose wastewater contains several hazardous or toxic substances. From other facilities such as hospitals and other health care institutions, testing may be required if necessary, e.g. in the event of disturbances at the MWWTP.

- Liquids and solid waste originating from pharmaceutical products that contain pharmaceutical residues should not be allowed to discharge directly into the sewer system. They should be collected and transported separately - from other wastewater led into municipal sewers - to specific hazardous waste treatment plants or be properly pretreated before discharging into the municipal sewer. In accordance with their properties, some liquids can be classified as hazardous wastes and should be handled accordingly.

6. References

1. UNESCO and HELCOM. 2017. Pharmaceuticals in the aquatic environment of the Baltic Sea region – A status report. UNESCO Emerging Pollutants in Water Series – No. 1, UNESCO Publishing, Paris https://helcom.fi/wp-content/uploads/2019/08/BSEP149.pdf
2. Manufacture of Organic Fine Chemicals. BREF [WWW] https://eippcb.jrc.ec.europa.eu/reference/BREF/ofc_bref_0806.pdf
3. Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control). OJ L 334, 17.12.2010, p. 17
4. Frequently Asked Questions (FAQ). [WWW] https://ec.europa.eu/environment/industry/stationary/ied/faq.htm#annex1.4
5. Best Available Techniques (BAT) Reference Document for the Production of Large Volume Organic Chemicals [WWW] http://publications.jrc.ec.europa.eu/repository/bitstream/JRC109279/jrc109279_lvoc_bref2017(1).pdf
6. BAT Guidance Note on Best Available Techniques for Pharmaceutical and Other Speciality Organic Chemicals [WWW] https://www.epa.ie/pubs/advice/bat/BAT%20Guidance%20Note%20Pesticides%20Pharmaceuticals%20&%20Speciality%20Organic%20Chemicals.pdf
7. Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy. OJ L 327, 22.12.2000, p. 3-4
8. Updated surface water Watch List adopted by the Commission [WWW] https://ec.europa.eu/jrc/en/science-update/updated-surface-water-watch-list-adopted-commissionEuropean Medicines Agency (2018), Guideline on the environmental risk assessment of medicinal products for human use [WWW] https://www.ema.europa.eu/en/environmental-risk-assessment-medicinal-products-human-use#current-version-section
9. Loos, R., Marinov, D., Sanseverino, I., Napierska, D., Lettieri, T. (2018) Review of the 1st Watch List under the Water Framework Directive and recommendations for the 2nd Watch List. JRC Technical Report. [WWW] http://publications.jrc.ec.europa.eu/repository/bitstream/JRC111198/wl_report_jrc_2018_04_26_final_online.pdf
10. Council Directive 91/271/EEC of 21 May 1991 concerning urban waste-water treatment https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31991L0271&qid=1602079916788&from=ET
11. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32001L0083&qid=1602079602200&from=ET
12. European Medicines Agency (2018), Guideline on the environmental risk assessment of medicinal products for human use [WWW] https://www.ema.europa.eu/en/environmental-risk-assessment-medicinal-products-human-use#current-version-section
13. BIO Intelligence Service (2013), Study on the environmental risks of medicinal products, Final Report prepared for Executive Agency for Health and Consumers [WWW] https://ec.europa.eu/health/sites/health/files/files/environment/study_environment.pdf

14. VICH GL6 Environmental impact assessment (EIAS) for veterinary medicinal products - Phase I (CVMP/VICH/592/98 -Final, 2000), Environmental impact assessment for veterinary medicinal products Phase ii guidance https://www.vichsec.org/en/guidelines/pharmaceuticals/pharma-safety/environmental-safety.html
15. Integrated permits [WWW] https://www.keskkonnaamet.ee/en/activities/integrated-permits
16. OECD (2005) Integrated environmental permitting guidelines for EECCA countries. [WWW] https://www.oecd.org/environment/outreach/35056678.pdf
17. Assessment of the current situation concerning industrial wastewater discharge into municipalwastewater systems in the Baltic Sea Region. Final report. 2020. The project BEST–Better Efficiency for Industrial Sewage Treatment https://bestbalticproject.eu/wp-content/uploads/2020/09/WP2_Assessment-of-current-situation_FINAL.pdf
18. Overview of pharmaceuticals regulatory environment in the Russian Federation [WWW] https://www.lexology.com/library/detail.aspx?g=88be4cd3-a1c7-4e68-b735-c16d3313f1f7
19. https://bclplaw.ru/en/actual/publication/84949/
20. Russia: Established procedure for issue, renewal, amending and revocation of integrated environmental permits [WWW] https://www.pravsky.com/russia-established-procedure-issue-renewal-amending-and-revocation-integrated-environmental-permits
21. European Medicines Agency. EudraMIA database [WWW] http://eudragmdp.ema.europa.eu/inspections/mia/searchMIA.do (last visited: 13.10.2020)
22. European Pharmaceutical Industry: Recent Trends and Statistics [WWW] https://www.ihealthcareanalyst.com/european-pharmaceutical-industry-recent-trends-statistics/
23. Regulation (EC) No 166/2006 of the European Parliament and the Council of 18 January 2006 concerning the establishment of a European Pollutant Release and Transfer Register and amending Council Directives 91/689/EEC and 96/61/EC. OJ L33/1, 04.02.2006
24. European Medicines Agency. EudraGMDP database [WWW] https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/eudragmdp-database (last visited: 13.10.2020)
25. Estonian Industrial Emissions Act [WWW] https://www.riigiteataja.ee/en/eli/511102017002/consolide
26. https://www.eesti.ee/et/ettevotja/keskkonnakaitse/keskkonnaload/
27. Danish Executive order on the Environmental Protection Act [WWW] https://www.retsinformation.dk/forms/R0710.aspx?id=202837
28. Estonian Medical Products Act [WWW] https://www.riigiteataja.ee/en/eli/508012018002/consolide
29. Estonian Agency of Medicines - Activity licenses database [WWW] http://rkav.sm.ee/rkav/faces/pages/tegevuslubaForm/tegevuslubaOtsing.jspx
30. Äystö, L., Mehtonen, J., Vieno, N., Ahkola, H., Leppänen, M., Sikanen, T., Yli-Kauhaluoma, J. & Nystén, T. 2019. Lääkeaineet lääketeollisuuden ympäristöluvissa. SYKEn raportteja 20/2019.
31. Farmaceitiskās darbības uzņēmumu reģistrs: https://www.zva.gov.lv/zvais/fdu-registrs/?lang=lv&q=&lic%5B%5D=afv&addr-n=&addr-c=&addr-s=
32. Estonian Government Regulation No. 99 [WWW] *(in Estonian)* https://www.riigiteataja.ee/akt/116122016006
33. HELCOM Recommendation 28E/5 [WWW] http://www.helcom.fi/Recommendations/Rec%2028E-5.pdf
34. Finnish Water Utilities Association (2018) Finnish Industrial Wastewater Guide [WWW] https://www.vvy.fi/site/assets/files/2179/finnish_industrial_wastewater_guide.pdf

35. Estonian Ministry of Environment regulation No. 18 [WWW] *(in Estonian)* https://www.riigiteataja.ee/akt/107052013024
36. Äystö, L., Laitinen, J., Vieno, N., Nystén, T., Fjäder, P., Kandelberg, K. 2020. Lääkejäämien esiintyminen sairaalajätevedessä – Tapaus TYKS. Ympäristö ja terveys 4/2020: 70-75.
37. Ort, C., Lawrence, M. G., Reungoat, J., Eaglesham, G., Carter, S., & Keller, J. 2010. Determining the fraction of pharmaceutical residues in wastewater originating from a hospital. Water Research, 44(2): 605–615.
38. Niemi, L., Taggart, M., Boyd, K., Zhang, Z., Gaffney, P. P. J., Pfleger, S., & Gibb, S. 2020. Assessing hospital impact on pharmaceutical levels in a rural 'source-to-sink' water system. Science of the Total Environment, 737(May).
39. Sörengård, M., Campos-pereira, H., Ullberg, M., Yin, F., Golovko, O., & Ahrens, L. 2019. Mass loads, source apportionment , and risk estimation of organic micropollutants from hospital and municipal wastewater in recipient catchments. Chemosphere 234: 931–941.
40. Santos, L. H. M. L. M., Gros, M., Rodriguez-mozaz, S., Delerue-matos, C., Pena, A., Barceló, D., & Montenegro, M. C. B. S. M. 2013. Contribution of hospital effluents to the load of pharmaceuticals in urban wastewaters : Identification of ecologically relevant pharmaceuticals. Science of the Total Environment, 461–462: 302–316.
41. Langford, K. H., & Thomas, K. V. 2009. Determination of pharmaceutical compounds in hospital effluents and their contribution to wastewater treatment works. Environment International, 35(5): 766–770.