Platform to enable the initiation of a revision of EU legislation on Good Manufacturing Practice, GMP, in order for legislation also to comprehend environmental considerations

Report from the Medical Products Agency

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Sustainable development in the pharmaceutical sector is gaining ground. In recent years our understanding of the connection between health and the environment, that is, that a good environment is a precondition for good public and animal health, has grown. This is gratifying, and it facilitates the mission of the Medical Products Agency to focus, support, and advance the field.

Pharmaceutical companies are taking bold initiatives, both independently and through their sectorial associations. A key issue has been "green pharmaceutical production" and bringing about improved manufacturing conditions in low-cost countries. When Swedish research findings showed that emissions from drug manufacturing in India can seriously affect our health and environment, through increased risk of multi-resistant bacteria strains, for example, the pharmaceutical industry contacted the government to launch efforts to address this issue. This initiative led to the Medical Products Agency receiving commissions from the government, in 2009 and 2011, to draw up a platform to enable Swedish initiatives leading to greater consideration for the environment in global pharmaceutical production. This work was to contribute to the overarching objective in environmental policy of handing over to the next generation a society in which the major environmental problems of Sweden have been solved, without causing environmental and health problems beyond Sweden’s borders.

With drug production being relocated and emissions appearing in the third world, it is important for Sweden to impel the EU to undertake forceful measures. Sweden possesses great knowledge and enjoys a high level of trust in the spheres of medicinal products and the environment. Moreover, Sweden boasts one of the largest aggregate research commitments in the field through the work of the research foundation MistraPharma, where the Agency has played an active role in the work of both the reference group and the board. The objective is to identify what pharmaceutical substances in use today constitute a substantial risk to our water environments, and to draw up recommendations and technologies for enhanced treatment of medicinal products in wastewater. A major part of MistraPharma’s coming work will be focused on the spread of antibiotic-resistant bacteria as a result of production emissions, a question where the connection between health, the environment, and the economy is highlighted very clearly.

When the Amsterdam Treaty came into force in 1999, sustainable development became a goal on a par with economic and social development, and environmental considerations must be integrated into all EU activities – an environmental policy that also comprises sustainable development for medicinal products, which is now beginning to be reflected in the initiatives being pursued in the area. Work for cleaner drug production yields a major favourable impact on public health. The connection between public health and the environment was elucidated by the Commission in its communication COM 2008 (666), where its concern is expressed in the following manner: “Pollution of waters and soils with pharmaceutical residues is an emerging environmental problem and also an emerging public health concern” and “It is now necessary to focus on measures that could reduce the potentially harmful impact of medicinal products on the environment and public health.” In the communication an objective was formulated stating that measures to reduce the possible harmful effects of medicinal products on the European environment and public health needed to be proposed. Thereafter the Commission, through work to revise EU legislation regarding
safety monitoring of medicinal products, has been urged, on the basis of information from Member Countries, for example, to compile reports about the problem of pollution of soils and waters with pharmaceutical residues and to determine whether EU legislation needs to be changed. A further initiative in this field is the EU’s Baltic Strategy, in which efforts in the area of the environment and medicinal products will be initiated in the autumn of 2011, efforts that Sweden will be leading through the Medical Products Agency.

In work at the global level, the Medical Products Agency continues to strengthen its ties with its global sister agencies for collaboration in all aspects addressed by the Agency, not least in work for sustainable development. During 2011 our contacts are being intensified by e.g. visits to Brazil, India, and China for the purpose of establishing written agreements of understanding.

With the proposals presented in this commission, and against the background of developments in the last year, I am extremely hopeful that together we will achieve the objective of sustainable development for medicinal products, thereby attaining production that is environmentally, economically, and socially defensible wherever in the world it occurs.

I wish to thank my associates at the Medical Products Agency, the Swedish Chemicals Agency, the Swedish Environmental Protection Agency, the Swedish Environmental Research Institute, the Environmental Committee of the Research-based Pharmaceutical Industry (LIF) trade association, and AstraZeneca for their excellent collaboration.

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Summary and proposals

The government’s commission to the Medical Products Agency is, after consultation with the Swedish Chemicals Agency and the Swedish Environmental Protection Agency, to draw up a platform to enable a revision of EU legislation regarding Good Manufacturing Practice, GMP, in order for the legislation also to comprehend environmental considerations, if this is found suitable. The commission is to take its point of departure in the Agency’s report from the government’s commission regarding the possibility of tightening environmental regulations for the manufacturing of medicinal products and active substances (governmental allocations and assignments for the Medical Products Agency, 2009). In the final report to be submitted by June 30, 2011, the Agency must develop concrete proposals for changes in GMP legislation.

Today a considerable share of pharmaceutical manufacturing and production of starting materials and semi-products takes place in low-cost countries, and many large companies plan to locate even more of their production there. In the first decade of the 21st century, Swedish research findings have revealed emissions from the manufacturing of medicinal products in India on a scale that can seriously impact the health of humans and animals, as well as the environment. Against this background, emissions of pharmaceutical substances from drug production in the third world are an urgent matter.

The proposals presented by the Medical Products Agency in this report make it possible to control environmental emissions of substances stemming from pharmaceutical manufacturing whose discharge it is especially urgent to reduce, including both human and veterinary medicinal products.

Anyone granted authorization to manufacture medicinal products must comply with a number of requirements under current legislation. One of these is to conform to the principles and guidelines of Good Manufacturing Practice, GMP, for medicinal products, thereby using as starting materials only active substances that were produced in accordance with detailed guidelines for good manufacturing practice for starting materials. Good manufacturing practice is a component of the quality assurance that is intended to make sure that the products are always produced and monitored in such a manner that they satisfy quality requirements that are appropriate for their intended use. Manufacturing authorization will be revoked if, for example, GMP is not observed.

By inserting the regulations for environmental control among production regulations within the framework of GMP, legislation will also have an impact on third countries. A further advantage of placing environmental requirements within GMP is that there is a well-developed and well-functioning inspection system for monitoring manufacturing and GMP. By placing environmental requirements within the framework of GMP, inspection rules will also apply to checking that environmental requirements are being observed. The report contains the following four proposals: (For more detailed information and rationale, see Chapter 5.)

1. Among directives regarding medicinal products an obligation is added for manufacturers of medicinal products to comply with the requirements in a separate legal document, a new EU regulation (see item 2 below), in which emission levels for certain substances are stated. The new obligation among
pharmaceutical directives should be inserted in the requirement to comply with GMP in production.

2. A new EU regulation should be created. The aim in proposing a new legal document is that it should stipulate the pharmaceutical compounds that need to be controlled in terms of emissions from production as well as the emission levels that are not acceptable. To found a good structure for the proposed regulation the cosmetics legislation in the EU might be followed.

3. What should receive top priority for a first step in the above-mentioned EU regulation are those pharmaceutical substances for which there is scientific evidence that the external environment, and thereby public health, is negatively impacted. First and foremost this concerns antibiotics, certain medicinal products with hormone-disrupting substances, and substances that can constitute a risk to the environment in that they are used and produced in large volumes.

4. The new EU regulation should establish a procedure for how to identify further substances and how to determine concentration limits. These concerns will need to be addressed by some EU body that has the relevant environmental expertise.
1 Introduction

1.1 The commission

1.1.1 The government’s commission

In its 2009 allocations and assignments from the government, the Medical Products Agency was commissioned, in consultation with the Swedish Environmental Protection Agency and the Swedish Chemicals Agency, to chart the possibility of tightening environmental requirements in the manufacturing of medicinal products and active substances for medicinal products, in Sweden and abroad. The possibilities of legislation as well as voluntary industry initiatives and/or global initiatives at the UN level were to be investigated and different options proposed.

In December 2009 the Medical Products Agency submitted eight proposed measures to the government. The main proposal presented was to require environmental certification of production facilities as follows:

As a first priority the government should work for a revision of the directives regulating Good Manufacturing Practice, GMP, for human medicinal products, 2003/94/EC, and veterinary medicinal products, 91/412/EEC, so that they include requirements for environmental considerations in the production of medicinal products. The requirement of environmental certification for production facilities for the manufacture of medicinal products and active substances should be incorporated into legislation regarding good manufacturing practice for the purpose of ensuring that GMP also includes an environmental perspective. The details of such certification should be investigated further.

In its 2011 allocations and assignments, the Medical Products Agency was given the following commission from the government:

The Medical Products Agency is commissioned, in consultation with the Swedish Chemical Agency and the Swedish Environmental Protection Agency, to create a platform to enable the initiation of a revision of EU legislation on Good Manufacturing Practice, GMP, if it is deemed suitable, in order for the legislation also to comprehend environmental considerations. The point of departure for the commission is to be the Agency’s report from its governmental commission regarding the possibility of tightening environmental requirements for the production of medicinal products and active substances (allocations and assignments for the Medical Products Agency, 2009). The commission is to be reported in two steps as follows:

Taking an EU perspective as its point of departure, for example in a dialogue with EU institutions, the Medical Products Agency is to present an analysis of how work to revise GMP legislation should be structured to have the greatest possibility of succeeding. This assignment is to be reported by 31 March 2011.

Further, the Agency is to develop concrete proposals for changes in GMP legislation. This assignment is to be reported by 30 June 2011.
1.1.2 Delimitation and implementation

The investigation has primarily focused on proposing measures to prevent environmental problems in connection with the production of medicinal products. The use of medicinal products can also cause environmental problems, for example when hormone-disrupting substances reach water systems through wastewater following use.

The environmental problems stemming from the use of medicinal products are very important, but they are also complex and considerably more difficult to deal with compared with preventing emissions from the production of medicinal products. The use of medicinal products is therefore treated only briefly in the report. This is also the case regarding public procurement of medicinal products, which can be a steering instrument also for better environmentally adapted manufacturing. However, proposals in these areas were not included in the commission.

The Medical Products Agency has carried out the government’s commission in consultation with the Swedish Chemicals Agency and the Swedish Environmental Protection Agency. A reference group, headed by Charlotte Unger, Medical Products Agency, has consisted of Ingrid Jedvall and Bo Carlerup, Swedish Environmental Protection Agency, Stefan Gabring and Eva Nilsson, Swedish Chemicals Agency, and Christer Backman, Staffan Castensson, Tor Gråberg, Pernilla Löthberg, Gert Ragnarsson, Carina Carlsson, and Luisa Becedas from the Medical Products Agency. Christina Brandt, Medical Products Agency, has been the project assistant. This report focuses on the second step in the commission. Discussions have been carried out primarily with the Astra Zeneca company, on the advice of the Environmental Committee at the industry association LIF (Research-based Pharmaceutical Industry). The purpose, among others, was to get a picture of how pharmaceutical companies work with pharmaceutical manufacturing and their thoughts regarding more requirements concerning emissions from production.

1.2 Background

1.2.1 Medicinal products are spread via use and production

Over the last decade pharmaceutical production has increasingly been relocated outside the borders of Sweden and Europe. Today a major share of manufacturing takes place in China, India, etc.

In 2007 Joakim Larsson’s research team at Gothenburg University published a study of the concentrations of medicinal products in purified wastewater from a purification plant in Patancheru outside Hyderabad in India. The pharmaceutical substances produced in the area are largely exported to Europe and the United States, among other markets.

The purification plant (PETL: Patancheru Enviro Tech Limited) studied receives process water from some 90 neighbouring pharmaceutical manufacturers. The concentrations of a great number of medicinal products in the purified water were much higher than had ever been reported anywhere in Swedish municipal wastewater. The pharmaceutical that was found in the highest concentration, ciprofloxacin, a broad-spectrum antibiotic that does not readily break down in nature was metered at concentrations of about 30 mg/L. This is nearly a million times more concentrated than what is found in purified water from Swedish purification plants, for instance, and the
level is even higher than what is found in the blood of a patient being treated with the pharmaceutical. The amount of ciprofloxacin that was calculated to be emitted from the purification plant in one day was 45 kg, which can be compared with Sweden’s total daily consumption of 9 kg for this pharmaceutical.¹

A follow-up study of samples taken some 1.5 years later showed once again that several medicinal products were found in very high levels in the purified wastewater. Very high concentrations of medicinal products were found downstream from the purification plant, but also in two small lakes nearby that are not downstream from the purification plant. Thus there were further sources of highly elevated levels of medicinal products in the area. One possible source was one or more of the more than 40 illegal dumping sites for industrial waste that local authorities had previously reported.

The studies also showed that well water was contaminated by several different medicinal products. The medicinal products had thus spread to the groundwater in the region. However, the concentrations of medicinal products in well water were not so high that any direct impact on humans drinking the water could be expected, but the risk of resistance development was pointed out.

The production chain for medicinal products is often long, comprising a number of steps involving multiple companies and countries. The chain includes everything from the production of starting materials, which can be e.g. petroleum products, minerals, and various nature products, further processing of intermediaries, synthesis of active pharmaceutical substances to the formulation and production of pharmaceutical preparations, packaging, and distribution. From the stage involving the production of substances and later in the chain, there is a risk that specifically active pharmaceutical substances can reach the environment.

In summary, this shows that medicinal products are spread not only via their use but also in their production in a way that is palpably harmful to the local environment and contributes to the global problem of antibiotic resistance (Figure 1.)

1.2.2 Antibiotic resistance – a borderless problem

The fact that bacteria are developing resistance to antibiotics is one of the greatest public health problems of our time. The lack of effective antibiotics hampers and delays the treatment of commonly occurring infections both in both in- and outpatient care and is a growing threat to public health. Longer care times and increasing costs for care constitute a major burden on the already strained economy of health care.

When it comes to emissions of antibiotics, besides their direct effects on e.g. local microbial societies, there is also an indirect risk to us humans. The risk is that emissions, in the absence of advanced purification, further the development and spread of resistant bacteria. This is a problem that has received attention both in Sweden and in other countries, as most purification plants today are not adapted to deal with antibiotic residues. Many antibiotics degrade only slowly in nature and thereby retain their active form for a long time. Resistant, pathogenic bacteria are tending to spread throughout the world, even though this spread can be slowed down by various measures. Whether resistance develops in Sweden or globally makes little difference in the long run. In other words, the potential consequences of antibiotic emissions recognize no boundaries. It is clear that the rapid development of resistance globally is a result of the extensive and often improper use of antibiotics. In recent years antibiotic residues in the environment have been found to be an ever-greater possible risk factor for the development of resistance alongside antibiotic usage for humans and animals.

Emissions from production can aggravate the situation with antibiotic resistance. One example is the purification plant PETL in India, where “active sludge purification” is used, a common technology at many purification plants whereby bacteria from the end of the process are returned to a previous purification step. One reason to use active sludge purification is to favour precisely those bacteria that can live off the nutrition found in the incoming water, which thereby makes purification more effective. On the other hand, if the incoming water contains very high concentrations of various antibiotics, active sludge purification entails a pronounced selection of highly resistant bacteria strains.

The EU and WHO rank the rapid development of antibiotic resistance as one of the three greatest threats to human health. Their work focuses on appropriate therapeutic use of antimicrobial medicinal products in human and veterinary medicine, the prevention of both care-related and socially acquired infections by resistant bacteria, and strategies to improve the development of new antibiotics.

1.2.3 Other problematic medicinal products

In production and/or use of certain medicinal products, unacceptable environmental effects can arise, constituting a threat to public health and biological diversity when the substances reach the water environment. Besides medicinal products containing antibiotics, problems have been identified for a number of hormonally and anti-inflammatoryly active medicinal products.

Substances that affect hormonal systems have attracted attention over the last few years, as they can cause serious harm to organisms, populations, or ecosystems. Hormone-disrupting substances are discussed, for example, in connection with health
issues like certain cancer forms, precocious puberty in children, increased frequency of malformed sex organs, deteriorated sperm production and sperm quality in men, and obesity, diabetes, and behavioural disturbances. Hormone-disrupting substances receive special attention in the “Action Plan for Zero Toxins in Daily Life” that the government commissioned the Swedish Chemicals Agency to devise in December 2010, to apply to the period 2011–2014. At the EU level work is underway to deal with the risks posed by these substances through various legislative acts, including the EU’s chemicals legislation Reach and pesticide legislation. Internationally, there is work being done within UNEP/WHO where an update has been initiated regarding “the Global assessment of the State-of-the-Science of Endocrine disruptors (1992).” Malformations and impaired reproductive capacity caused by exposure to hormone-disrupting substances have been reported for several different animal groups. Progestins, hormone preparations used in contraceptives, in cancer treatment, in menopause treatment are examples of hormonally active medicinal products that reach the environment via our wastewater systems. Recently researchers have shown that the progestin levonorgestrel, the active substances in last-minute contraceptives, etc., can cause sterility in frogs at levels that are close to those found in our environment. This shows that medicinal products other than oestrogens can lead to permanent harm in aquatic animals.2

The pharmaceutical diklofenak, an anti-inflammatory medicine used for both animals and humans began to be given largely for preventive purposes to cattle in India and Pakistan in the late 1980s. Soon after, in the early 1990s, Indian ornithologists discovered that vultures were beginning to disappear at an alarming rate. More detailed studies showed that the birds were dying of kidney failure, and in 2004 an American research team were able to establish that this kidney failure was caused by diklofenak. Vultures in southern Asia live mainly on cows and buffalo that had died a natural death. In this way they ingested large amounts of the pharmaceutical each time they ate. The new study, published in Journal of the Bombay Natural History Society, shows that the originally most plentiful species, the Asian white-backed vulture, has declined by 99.9 per cent since 1992, from more than 10 million to 11,000 birds. The other two species affected, the long-billed vulture and the slender-billed vulture, have together diminished 96.8 per cent, from 1.5 million to 46,000 individuals. The researchers point out that hardly anything like this has ever been registered before. It is probably the most rapid decline to affect individual animal species since the latest ice age.

To acquire enhanced knowledge of the field, research is underway both within the medicinal products industry and within other organizations, such as the environmental research foundation Mistra’s programme for medicinal products, MistraPharma. The objective for MistraPharma is to identify medicinal products that constitute a substantial risk to aquatic organisms, to make recommendations for improved sewage purification, to propose strategies for early identification of medicinal products that pose a threat to aquatic species, and to strengthen the network between researchers and stakeholders in the field (www.mistrapharma.org).

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2 Grabic, Brant I and Berg C (2011). Early life progestin exposure caused oocyte development, oviductalagenesis and sterility in adult Xenopus tropicalis frog. Aquatic Toxicology. 2011 02.003
1.2.4 Sustainable development for medicinal products

The goal of Swedish environmental policy comprises both the environment and health

The overarching goal of Swedish environmental policy is to pass on to the next generation a society where the major environmental problems of Sweden have been solved, without causing environmental and health problems outside Sweden’s borders (the generation goal).

This is predicated upon an ambitious environmental policy in Sweden, within the EU, and in international contexts. The generation goal entails that the preconditions for solving environmental problems must be achieved within one generation and that environmental policy must focus on:

- ecosystems having recovered, or being on the road to recovery, and their capacity to generate long-term ecosystem services having been ensured
- biological diversity and the natural and cultural environment having been preserved
- people’s health being exposed to minimal negative environmental impact while at the same time positive impacts of the environment being promoted
- circulating systems being resource effective and as far as possible free of hazardous substances
- economic use of natural resources
- the proportion of renewable energy increasing and energy use being efficient with minimal impact on the environment
- consumption patterns for goods and services causing as few environmental and health problems as possible.

1.2.5 Today’s legislation is inadequate

Both medicinal products legislation and environmental legislation are areas that evince strong or very strong influence from EU legislation. A point of departure for EU law is the Brundtland Report’s goal of sustainable development, which is especially emphasized in Article 3 (3) of the EU Constitution, the Treaty of Lisbon3): “The Union shall establish an internal market. It shall work for the sustainable development of Europe based on balanced economic growth and price stability, a highly competitive social market economy, aiming at full employment and social progress, and a high level of protection and improvement of the quality of the environment. It shall promote scientific and technological advance.”

EU pharmaceutical legislation regarding authorization of medicinal products presently allows no scope to establish environmental requirements relating to production. Environmental legislation today comprises various types of emissions from industry but more in the form of aggregate parameters than individual substances, and at present there is no self-evident way to regulate emission of individual pharmaceutical substances from the pharmaceutical industry.

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The work that most clearly touches on pharmaceutical emissions into the water environment today is the EU Framework Directive for Water. On a list of proposed priority substances, that is, substances that constitute a significant risk to the water environment, there are four pharmaceutical substances. Two hormones, 17 beta oestradiol, a natural oestrogen produced by humans and animals, and 17 alpha ethinylestradiol, a synthetic oestrogen used in contraceptives and other types of hormone treatment, along with two anti-inflammatory pharmaceutical substances, diklofenak and ibuprofen.

The picture of the problem and the lack of relevant legislation indicate the need for measures at the EU level that also reaches countries outside the Union.
2 Regulatory documents

2.1 Delimitation and background
The report takes up pharmaceutical legislation and environmental legislation, as these legal areas look in the EU, within the framework of what is relevant to the government’s commission. From a legal point of view, the matter of risks related to emissions from industrial activity is neither new nor unique to the pharmaceutical industry. However, emissions from the pharmaceutical industry entail special disturbances to the environment and to human health.

A special circumstance for this task is that the production of medicinal products and active substances, and thereby emissions thereof, largely takes place in countries other than those in which the majority are consumed. Production is also carried out mainly on commission from companies that are not legally domiciled in the producing countries. Production often occurs in developing countries. A highly relevant question is therefore what the possibilities are in a legal perspective to affect production in third countries.

A fact of crucial importance to the proposal to work for a revision of the directives that regulate Good Manufacturing Practice, GMP, so that they include requirements to take the environment into consideration in the production of medicinal products, is that companies must be able to demonstrate that their products are manufactured in accordance with GMP in order for the product to be receive a marketing permit (authorization) in Europe.

The description of EU legal regulation of medicinal products below has been designed to increase understanding for the proposal presented in Chapter 4. The focus thus lies on regulations of significance for the proposal.

2.2 Medicinal products legislation

2.2.1 The central legal documents
The two medicinal products directives are largely set up along the same lines, and articles with the same content are frequently found in both directives. In references to the articles below, the article in Directive 2001/82/EC is given first and then the article in Directive 2001/83/EC.

Norway, Iceland, and Liechtenstein are not members of the EU but have pledged to comply with the regulations in the medicinal products directives. What is said below about the EU and its Member Countries thus applies to these countries as well.

2.2.2 Authorization requirements for manufacturing and marketing within the EU

According to the medicinal products directives authorization is required from some competent pharmaceutical authority in the EU to manufacture and market medicinal products within the EU. For those wishing to manufacture medicinal products, requirements to be granted authorization for this are stipulated, as well as what requirements a prospective manufacturer must satisfy. The directives also regulate what requirements are placed on an application for authorization to market medicinal products, as well as what obligations a marketing authorization holder, an MAH, has. The requirements are numerous and comprise, for instance, compiling and following up reports on side effects and staying abreast of scientific and technological developments and taking measures to ensure that the pharmaceutical can be produced and monitored using generally accepted methods.

The manufacturer of the pharmaceutical need not be the same person as the one applying for authorization to market the pharmaceutical. If this is not the case, the person applying for authorization must show that he/she contracts only with manufacturers who have authorization to produce medicinal products.

![Diagram](https://example.com/diagram.png)

Figure X. Conditions for having a pharmaceutical authorized for marketing.

2.2.3 Manufacturing of medicinal products

As indicated above, to be allowed to manufacture medicinal products authorization is required under the medicinal products directives (Arts. 44 and 40, respectively). Such authorization is necessary regardless of whether the production regards the whole or parts of the pharmaceutical, certain steps in the production process, or various procedures for dividing, packing, or packaging/presentation. Manufacturing authorization may cover certain medicinal products or apply to all medicinal products in general. Manufacturing authorization is required also to import medicinal products from third countries. The sections in the directives that regulate production also apply to imported medicinal products. Thus the same manufacturing requirements are placed on medicinal products regardless of where their production takes place. The competent
authorities in the countries that have issued production authorizations within the EU carry out inspections of production sites with the support of the directives, see Arts. 80 and 111, respectively. This also applies to production sites in third countries.

2.2.3.1 Good Manufacturing Practice (GMP)

Those granted authorization to manufacture medicinal products must comply with a number of requirements delineated in the directives. One of these is to comply with the principles and guidelines for Good Manufacturing Practice, GMP, for medicinal products and thereby to use as starting materials only active substances that have been produced in accordance with detailed guidelines for good manufacturing practice for starting materials (Arts. 50 f and 46 f, respectively).

In Arts. 51 and 47, respectively, the Commission is directed to adopt as directives the principles and guidelines for good manufacturing practice referred to in Arts. 50 and 46, respectively. As a result of this, the Commission adopted Directive 91/412/EEC on the adoption of principles and guidelines for good manufacturing practice regarding veterinary medicinal products and Directive 2003/94/EC on the adoption of principles and guidelines for good manufacturing practice regarding human medicinal products and trial medicinal products for human use. The Commission is also delegated power in said articles to adopt detailed guidelines for good manufacturing practice for active substances used as starting materials. Such guidelines have also been adopted. 4

In Art. 2 in both Commission directives on GMP there is a definition of good manufacturing practice. Good manufacturing practice means the part of quality assurance that ensures that products are consistently produced and controlled in accordance with the quality standards appropriate to their intended use.

Under the medical products directives, manufacturers’ compliance with regulations for production and GMP is to be inspected by the competent authorities, Arts. 80 and 111, respectively. If there are deficiencies in compliance with good manufacturing practice, these authorities can issue a so-called “non-compliance GMP certificate.” This certificate is published in a joint EU database, EudraGMP, so that the information will be disseminated to all Member Countries. Inspections carried out in EU Member Countries are entered into this database on a continuous basis. These include inspections performed both within and outside the territory of the inspecting Member Country. See Arts. 80.6 and 80.7 and. Arts. 111.6 and 111.7, respectively.

Under Arts. 85.2 and 118.2, respectively, in the medicinal products directives, manufacturing authorization may be revoked for non-compliance with GMP, among other reasons.

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2.2.4 Authorization of medicinal products for sale

For a medicinal product to be sold in a Member State, besides being manufactured in accordance with what has been stated above, the medicinal product must be authorized in the Member State. Authorization may either be issued in accordance with one of the medicinal products directives (2001/82/EC and 2001/83/EC) or in accordance with Regulation (EC) No. 726/2004, see medical products directives Art. 5.1 and Art. 6.1, respectively. Authorization is thus necessary for a medicinal product to be marketed. There are some exceptions to this general rule, but they are insignificant in this context.

2.2.4.1 Authorization under the medicinal products directives

If someone wanting to have a medicinal product authorized for sale applies for authorization under the medicinal products directives, he must decide how comprehensive the authorization is to be. The medicinal product can either be authorized in a Member State or one of the two Community procedures leading to authorization in several Member States can be used.

The first Community procedure, the decentralized procedure (DCP), applies to new medicinal products that are not authorized anywhere in the EU. Application for authorization is submitted to the medicinal products authorities in those Member States in which the authorization is sought. The applicant chooses how many and which countries are to be included in the procedure. One of these Member Countries is selected as the reference Member Country. The authority in the reference Member Country is responsible for scrutinizing the application and leading the procedure forward to authorization or rejection (Arts. 32.1 and 32.3-5 and Arts. 28.1 and 28.3-5, respectively).

The other Community procedure, the mutual recognition procedure, MRP, is applicable when the medicinal product is already authorized in one (or more) Member States and the applicant wishes to have authorization in one or several more Member States. As with DCP, the applicant decides how many and which countries are to be
involved in the procedure. The country that has already authorized the medicinal product is the reference Member State with the same responsibility as in DCP. If the medicinal product has already been authorized in multiple Member States, the applicant selects which of these is to serve as the Reference Member State (Arts. 32.1-2 and 31.4-5 and Arts. 28.1-2 and 28.4-5, respectively). This procedure is compulsory in cases where a medicinal product has been authorized somewhere within the Community.

The third alternative under the medicinal products directives is to apply for authorization in a Member State by national application, the national procedure. This means that the application is submitted only to one Member State, and the application is consequently scrutinized and assessed by that Member State alone. A precondition for this option is that the medicinal product in question has not already been authorized in any other Member State, as the procedure for mutual recognition is then compulsory.

2.2.4.2 Authorization under Regulation (EC) No. 726/2004

Authorization granted following application according to (EC) No. 726/2004 takes force in all countries within the EU (Regulation Arts. 13.1 and 38.1). Thus the applicant does not choose which countries are to be included in the application (cf. the procedures under the medicinal products directives). The authorization process under the Regulation is called the Central Procedure. For certain medicinal products it is obligatory to apply for authorization under the Regulation (Art. 3.1). This regards medicinal products included in the list in the annex to the Regulation. The annex comprises, e.g., medicinal products produced using certain biotechnological processes and medicinal products containing a new active substance and intended for treatment of certain listed diseases, such as cancer, neurodegenerative disorders, and acquired immune deficiency syndrome. Under Art. 3.2 in certain cases an applicant may choose to apply for authorization under the Regulation for medical products that are not included in the annex.

For application under the Regulation, the application for authorization is submitted to the European Medicines Agency, EMA. At the Agency there is one committee for human medicinal products and one for veterinary medicinal products. These committees compose statements that serve as a basis for the final decision, which is made by the Commission. As mentioned above, such a decision has force in all Member States. If the application is denied, this constitutes a prohibition against releasing the medicinal product onto the market anywhere in the Community (Regulation Arts. 12.2 and 37.2).

2.2.4.3 Documentation requirements in applications for authorization to sell in regard to the environment

The documentation to be included in an application to have a medicinal product authorized is the same regardless of which procedure is used. What documentation is to be included is stated in Arts. 12.3 and 8.3, respectively, in the medicinal products directives. Documentation requirements for veterinary and human medicinal products differ, so the two directives are presented separately below. In Regulation (EC) No. 726/2004 it is stated in Arts. 6.1 and 31.1 that application for authorization of medicinal products under the Regulation must contain documentation as stated in Art. 8.3 in Directive 2001/83/EC for human medicinal products and Art. 12.3 in Directive 2001/82/EC for veterinary medicinal products, respectively.

2.2.4.3.1 Application for authorization under Directive 2001/82/EC
Under Art. 12.3 application for authorization of veterinary medicinal products must contain the information listed in the article. The following information regarding the environment must be submitted in the application:

12.3 g) reasons for any precautionary and safety measures to be taken when storing the veterinary medicinal product, administering it to animals and disposing of waste, together with an indication of potential risks that the veterinary medicinal product might pose to the environment, to human and animal health and to plants.

12.3 j) results of tests assessing potential risks posed by the medicinal product for the environment; this environmental impact must be studied and consideration shall be given on a case-by-case basis to specific provisions seeking to limit it.

In assessing an application for authorization for the sale of a veterinary medicinal product the risk/benefit ration for the medicinal product must be judged. Risk in connection with the use of a medicinal product is defined in the veterinary directive as any risk relating to the quality, safety and efficacy of the veterinary medicinal products as regards animal or human health and any risk of undesirable effects on the environment, Art. 1.19. In evaluating the risk/benefit ratio, the risks stated in Art. 1.19 must be weighed against the positive therapeutic effects that a medicinal product is deemed to have, see Art. 1.20. The result of this evaluation must be positive for the medicinal product to be authorized. Thus, for veterinary medicinal products, the risk of undesirable environmental effects is a circumstance that may lead to the medicinal product not being authorized for sale.

2.2.4.3.2 Application for authorization under Directive 2001/83/EC

Under Art. 8.3 application for authorization of a human medicinal product must contain the information listed in the article. The following information regarding the environment must be submitted in the application:

8.3 ca) Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged.

8.3 g) Reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment.

Also in assessing an application for authorization of a human medicinal product, the risk/benefit ratio must be judged. Risk in connection with use of a medicinal product is defined in the human medicinal products directive as any risk relating to the quality, safety or efficacy of the medicinal product as regards patients’ health or public health and any risk of undesirable effects on the environment, Art. 1.28. For human medicinal products, the risks of undesirable environmental effects are not to be weighed in when judging the risk/benefit ratio, see Art. 1.28a. Thus, the risk of undesirable environmental effects cannot cause a human medicinal product not to be authorized for sale.

2.2.4.4 Guidelines for performing an environmental risk assessment for the sale of medicinal products

2.2.4.4.1 Human medicinal products – focus on the water environment

Environmental risk assessment for human medicinal products comprises a comprehensive scientific evaluation that is done by the applicant company under
adopted European guidelines (EMEA/ CHMP/SWP/4447/00 corr 1). The guideline was adopted in its present working in June 2006 and now also contains a requirement to assess the properties of the active substance in regard to persistence (degradability), bioaccumulation, and toxicity (PBT) as well as a heightened requirement for long-term studies compared with earlier versions. This has enabled authorities, in their assessments after 2006, to achieve a better picture of the risks of negative environmental effects. On the other hand, environmental risk assessments performed prior to 2006 contain greater uncertainty owing to more incomplete data. The guideline is limited to environmental impact arising from using the product and not from storage, disposal, or production. As the greatest environmental exposure from use can be expected to occur through the secretion of active substances via urine and faeces that are then flushed into sewers, the assessment focuses on the water environment, taking water purification plants as its point of departure.

Environmental risk assessment following EMA’s guideline is done in multiple steps. First it is determined for all products whether the active substance has the potential to be stored in fatty tissues in animals (bioaccumulation) with the help of a laboratory measure of the substance’s distribution in a mixture of octanol and water (the so-called log Kow value). If the log Kow value indicates bioaccumulation, one proceeds with studies to elucidate the potential to persist for a long time in the environment (degradability studies, persistence), bioaccumulation studies in fish, and toxicity tests similar to environmental risk assessments for other chemicals and in accordance with guidelines from the former European chemicals authority, the European Chemicals Bureau.  

Further, for all products it is calculated what concentration of the active substance can be expected to be reached in surface water when the product is used in accordance with the product résumé, that is, the summary of a medicinal product’s properties and use that is authorized by the Medical Products Agency. If this concentration is below a general limit (0.01 µg/L) established in the guideline, it is concluded that use of the product is not expected to affect the environment, and the assessment is therefore completed. If the calculated effluent concentration to surface water exceeds the limit, the substance’s degradability, the division between water phase and sludge phase in the purification plant, potential effects on microorganisms in a purification plant, and ecotoxicological effects on aquatic organisms must be studied in a second step. Ecotoxicological studies required in this step comprise studies of growth, reproduction, and life cycles in algae, crustaceans, and fish. With the help of these data, it is calculated what concentration of the substance can be expected not to have a negative effect on the water environment, the Predicted No Effect Concentration (PNEC). If the estimated concentration in the water is greater than or equals PNEC, the risk assessment is refined by calculating the concentration in water, taking into account degradability data and computer simulation of what happens in a purification plant. This enables conclusions to be drawn about whether use of the product leads to unacceptable environmental consequences. In practice, the concentrations in water might be higher than the limits determined, as the assessments are done for one product at a time and the active substance may be found in multiple products on the market.

Sometimes the data show that the substance is expected to spread in sludge in the purification plant. As spreading sludge on agricultural fields can lead to exposure of soil-inhabiting organisms to medicinal products, eco-toxicological studies must also be

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carried out on soil-inhabiting organisms. If the substance spreads to sediment, eco-
toxicological studies must be performed on sediment-inhabiting organisms. With the
help of dedicated models, concentrations in soil and sediment are also calculated and
compared with PNEC for soil- and sediment-inhabiting organisms respectively. Here,
too, further refinements of calculations can be made or more advanced studies can be
used to eliminate or to identify a risk of environmental impact.

2.2.4.4.2. Veterinary medicinal products – focus on agricultural animals and
spreading to soil environment

The scientific assessment is technically more complicated than for human medicinal
products and is regulated in three guidelines (CVMP/VICH/592/98,
CVMP/VICH/790/03, EMEA/ CVMP/ERA/418282/2005-Rev.1). The assessment
begins with an estimation of how great the exposure in the environment may be for the
individual product. For products that are only to be used for pets or just a few animals
in a flock, it is assumed that exposure in the environment will be so limited that no
environmental impact is expected, and the assessment ends there. For other products
the concentration is estimated in fertilizer when the product is used in accordance with
the proposed dosage and frequency in the types of animals referred to in the
application. Further, the concentration is calculated in soil after fertilizer has been
applied or, alternatively, in grazing. It is also calculated what concentrations can reach
the groundwater via leaching. If the general limits established in the guidelines are
exceeded, the next step is to run degradability and eco-toxicological studies on soil-
inhabiting and aquatic organism. Here, too, calculations need to be refined stepwise
and/or more complex studies need to be carried out until it is possible to eliminate or
ultimately identify a risk of environmental impact.

2.2.4.5 Documentation requirements for applications for authorization for sale
regarding production

In Arts. 12.3 and 8.3, respectively, in the medicinal products directives, it is also
stipulated what applicants must present regarding production of the medicinal product
they wish to have authorized. Applicants must describe the method of production (Arts.
12.3 d and. 8.3 d, respectively) and the control methods the manufacturer applies (Arts.
12.3 i and 8.3 h, respectively) and must submit documents showing that the
manufacturer has the right to produce medicinal products in his/her home country
(Arts. 12.3 m and 8.3 k, respectively). This must be included in the application
regardless of whether it is the applicant who will produce the medicinal product or one
or more other actors will produce all or parts of the product.
2.2.5 Good manufacturing practice (GMP) – Global agreements

Requirements that can be placed according to good manufacturing practice (GMP) regarding production are designed to establish and ensure that medicinal products are manufactured in a quality assured manner. Current medicinal products legislation is not only harmonized within the EU; there is also close collaboration regarding GMP work between the EU and PIC/S (Pharmaceutical Inspection Co-operation Scheme), an association of currently 39 medicinal products authorities around the world. At present GMP is strongly harmonized between the two. In connection with making adjustments in EU-GMP and PIC/S respectively there is always a discussion at an early stage regarding how the planned change will be effected so that the views of other medicinal products authorities can be considered. This form of collaboration, with a dialogue with other authorities in which their views can be taken into consideration, is regulated in writing between EMA and PIC/S. This collaboration is designed to strengthen the possibility of changes in GMP being harmonized on a global level to the greatest possible extent. This integrated work at the global level lends further force to the impact of amended requirements and recommendations. Harmonized GMP regulations benefit both the medicinal products industry and medicinal products authorities.

There is also an exchange of information with WHO, which is the third principal actor with its own global GMP regulatory system.
Tying environmental requirements to the current EU regulatory system for good manufacturing practice also constitutes a first step towards achieving a broader reach for these requirements as a result of the global links that are in place regarding GMP. Furthermore, the tie between GMP requirements and authorization requirements to place a product on the EU market is potentially a powerful steering instrument.

2.2.6 New medicinal products legislation – the Directive on Counterfeit Medicinal Products

In 2011 the European Parliament and Council adopted amended legislation, the so-called Directive on Counterfeit Medicinal Products. The new directive entails amendments to Directive 2001/83/EC. Among other things, the changes strengthen the obligation to comply with GMP legislation. Those directly affected by the tightening of the legislation are manufacturers and marketing authorization holders within the EU but manufacturers in other countries are also indirectly affected.

Even prior to this new legislation marketing authorization holders within the EU have had to comply with the principles of good manufacturing practice and use only active substances produced observing good manufacturing practice. The new directive adds that they must ensure that the manufacturer and distributor of the active substances observe good manufacturing practice and good distribution practice by carrying out inspections of production and distribution sites of these manufacturers and distributors. The holder of the manufacturing permit must monitor this compliance, either on his own or through a party acting on his behalf.

Member States in the EU have a responsibility to ensure that active substances that are imported into the EU were manufactured under standards that are at least equivalent to those in effect within the EU. This requirement is satisfied by obliging the authority in the exporting country to confirm that good manufacturing practice is observed, that strict inspections are carried out regularly, and that the authority in the exporting country will notify the EU of any non-compliance.

The above obligation for confirmation may be waived if the exporting country is included in a registry kept by the European Commission. Third countries may request to be added to the registry, and the Commission assesses whether regulations in the exporting country are such that it is possible to ensure a level of protection comparable to that in the EU. This assessment often involves on-site inspections of facilities, but there is no requirement that all production sites in the country be inspected.

The amending directive will take force in the summer of 2013.

2.3 Environmental regulations

2.3.1 Introduction

Both medicinal products legislation and environmental legislation are areas that evince strong or very strong influence from EU legislation. A point of departure for EU law is the Brundtland Report’s goal of sustainable development, which is especially emphasized in Article 3 (3) of the EU Constitution, the Treaty of Lisbon: “The Union shall establish an internal market. It shall work for the sustainable development of Europe based on balanced economic growth and price stability, a highly competitive social market economy, aiming at full employment and social progress, and a high
level of protection and improvement of the quality of the environment. It shall promote scientific and technological advance.”

This section will deal with the EU’s chemicals legislation, the Reach Regulation. Then the IPPC Directive (Integrated Pollution Prevention and Control) and the IED Directive (Industrial Emissions [Integrated Pollution Prevention and Control])\(^6\) will be addressed. The latter two legal documents can be said to be a lowest common denominator for Member States’ legislation regarding emissions from major industrial facilities. After that the EU’s Framework Directive for Water\(^7\) will be treated, with its regulations affecting what may be emitted into wastewater, among other things. Finally, the discussion will move on to EU regulations regarding environmental impact statements,\(^8\) which are of essential importance in granting authorizations to industries and others.

### 2.3.2 The Framework Directive for Water

The EU Framework Directive for Water, 2000/60/EC, is intended to protect both inland and coastal waters as well as groundwater. The Directive comprises regulations that are important in terms of what may be emitted into wastewater. The Framework Directive further stipulates a combined approach for point sources and diffuse sources, with both emissions regulations and the introduction of environmental quality standards for certain priority substances. In Annex X of the Framework Directive there are currently 33 priority substances; none of these is a medicinal product. The Framework Directive also has a so-called subsidiary directive, 2008/105/EC. Annex II of the subsidiary directive is a list of environmental quality standards for the priority substances and is inserted into Annex X of the Framework directive. Annex II of the subsidiary directive contains priority substances that are to be the subject of review for possible identification. New substances are entered in Annex III of the subsidiary directive. Substances deemed to be priority substances following validation and identification are also inserted into Annex X of the Framework Directive. Member States are obligated to incorporate the content of the Directive in their national legislation, which here entails that environmental quality standards also apply to the new substances. The new substances may be medicinal substances.

The EU Commission, in collaboration with experts representing involved parties, has developed a system for establishing priorities using a combination of monitoring and models, called Combined Monitoring-based and Modelling-based Priority Setting (COMMPS). Through collaboration in COMMPS the current 33 substances in Annex X of the Framework Directive X have been selected. Every fourth year the EU Commission must review the list of priority substances. This autumn it is expected to present a proposal with further priority substances that it wants to include. The proposal will also contain environmental quality standards for these substances as well as changes in certain environmental quality standards for already listed priority substances. The proposal will then be negotiated in the Council and the European Parliament. Among the nearly 20 substances for which substance files and proposed environmental quality standards have been created there are four medicinal substances: two hormones, 17 beta oestradiol, a natural oestrogen produced by humans and

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\(^6\) The IPPC Directive will be phased out in two steps, in 2013 and 2014, and thereafter the IED Directive will have full force for all activities.


animals, and alpha ethinyloestradiol, a synthetic oestrogen used in contraceptives and other types of hormone treatment. The natural hormone accounts for 90% of emissions to surface water, whereas the synthetic represents less than 10%. Both hormones have significant effects on life in aquatic environments, such as feminization in fish, impact on reproduction and sexual development. Two anti-inflammatory medicinal substances are listed, diklofenak and ibuprofen. Whether or not these substances will be included in the Commission’s final proposal depends on, among other things, the Commission’s assessment of the impact analyses that were carried out when these substances were included.

A proposal being discussed by the work group for this governmental commission is to link GMP requirements for medicinal products to regulations on environmental quality standards for water via the Framework Directive for Water and its subsidiary directive. The idea is thus to counteract the emission into the water environment of priority substances (that is, the contents of certain medicinal products) listed in Annex X of the Framework Directive. Environmental quality standards apply generally to all activities in a Member State and not solely for producers of medicinal products.

If priority substances get into the water environment and their concentration rises, entailing a risk that environmental quality standards are exceeded, measures must be taken to reduce the concentrations so that the status the water had prior to the emissions is restored. Measures to be taken are to be established in a programme of measures. Such a programme of measures is to be adopted by the government or competent authority in a Member State and primarily be directed to local authorities responsible for monitoring. Those companies that produce medicinal products have authorization for their operations (cf. IPPC) and are therefore affected only indirectly by the programme of measures. Operations run under authorization must be protected from further requirements from the Member State. This means that the effect on outsourced production of medicinal products is even less than that on producers within the EU. The aim of being able to fully influence production companies in third countries would probably not be achieved by the GMP/environmental-quality-norm method. Other legal avenues must therefore be considered.

### 2.3.3 The Directive on Emissions from Industry

With the Swedish Environmental Code, a number of EU directives were incorporated into Swedish legislation. Among these is the Directive on Integrated Pollution Prevention Control, the IPPC Directive. Among other things, Member States are obligated to introduce regulations so that certain listed industries must have permission to be established.

Under Art. 3 the fundamental obligation in the Directive is that all appropriate preventive measures be taken to avoid pollution, especially through the use of best available techniques, BAT. In the Directive by pollution is meant: “direct or indirect introduction, as a result of human activity, of substances, vibrations, heat or noise into the air, water or land which may be harmful to human health or the quality of the environment, result in damage to material property, or impair or interfere with amenities and other legitimate uses of the environment.”

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10 Originally Directive 91/61/EC, subsequently changed to 2008/1/EC

11 Article 4.

12 Article 2.2.
The substitution principle finds expression in the IPPC Directive in that by establishing the best available technique, BAT, operators must consider the use of other substances that are less hazardous. In other words, it can be said that the EU law already includes requirements for industrial production of medicinal products to be preceded by an authorization procedure in accordance with environmental legislation, and considering the scope of the concept of pollution, the issue of emission of e.g. medicinal product residues and other types of medicinal products can be regulated through this authorization.

The Directive is a so-called minimum directive, which means that a Member State may have stricter regulations in its national legislation.

The European Parliament and Council have agreed to merge seven directives on industrial emissions into one. One of these seven is the IPPC Directive. The new directive, 2010/75/EU, the Industrial Emissions Directive (IED), came into force on 6 January this year. It must be incorporated into Swedish legislation by 7 January 2013 and then begin to be applied to new facilities. One year later it will also apply to existing facilities. IED entails stricter regulations for applying e.g. Best Available Technique (BAT) and minimum requirements for emissions from large incinerating facilities.

Under IED the Commission is to arrange an exchange of information among Member States, non-governmental environmental protection organizations, and the industries involved regarding BAT. The result of this exchange of information is to be reported in so-called BAT Reference Documents, BREF documents, for the various sectors of industry covered by the Directive. The medicinal products industry (pharmaceutical products, Chemical and biological processes) is included in a BREF document on Organic Fine Chemicals (OFC, August 2006). However, the document does not include any recommended emission levels for particular substances into water. Emission levels regarding polluting emissions into water are commonly formulated in the form of aggregate parameters as organic materials. The objective is for BREFs to be updated every eighth year.

Among the most important changes of relevance to the government’s commission, it can be mentioned that:

- Conclusions about what according to BAT Reference documents, BREFs, correspond to BAT for a sector must serve as a basis for establishing authorization conditions in each individual case
- Within four years following the adoption of a new BREF conclusion by the Commission, the conditions in individual authorizations must be updated, if necessary, and emissions must be below the levels stated as constituting BAT. There are certain limited exceptions possible.
- Authorizations must state how the conditions relate to the BAT conclusions.
- Monitoring requirements are clarified and made stricter. Among other things, all IED facilities must be inspected at least every third year, and large-scale facilities every year. An interesting change is that IED comprises facilities not only for medicinal products but also for semi-products.

Creating a new particular BREF for the medicinal products industry that manufacturers are obliged to follow takes time and involves a great deal of work. Such a new BREF would probably not be completed for four-five years. Today they are no plans (from EIPPCB in Seville) to create such a BREF.
As we see it, a BREF is not a self-evident route to follow for regulating emissions of particular medicinal substances from the medicinal products industry.

### 2.3.4 The Directive on Environmental Impact Statements

Under the Directive on Environmental Impact Statements\(^\text{13}\) Member States are obliged to introduce requirements for such statements in connection with authorization procedures for certain types of activity. In an environmental impact statement the applicant must give an account of a project including information on localization, construction, scope, hazards to human health and the environment, and a statement of planned measures to avoid, reduce, and if possible alleviate substantial harmful impacts.

The main rule is that production of medicinal products and use of a chemical or biological process in “integrated chemical facilities” are covered by the requirement for environmental impact statements. The production of pharmaceutical products must be the subject of such a statement when the Member States find it necessary owing to the nature of the project.

Existing companies within the EU that manufacture medicinal products have authorization and have provided environmental impact statements in connection with their applications for such authorization. To now introduce into the Directive on Environmental Impact Statements special regulations or stricter requirements for medicinal products manufacturers and to link these to GMP requirements for medicinal products would only affect new activities, not already established manufacturers.

The aim of ameliorating environmental aspects of manufacturing of medicinal products in third countries would probably not be achieved following this route; another solution must be sought.

### 2.3.5 EU chemicals legislation, Reach

In earlier commissions it was found that it is not probable that the EU’s chemicals legislation Reach (EC) No. 1907/2006 could be used to address environmental problems in connection with the production and use of medicinal products. Most sections of Reach exempt human medicinal products and veterinary medicinal products from its field of application. One section that can be applied deals with limits on the production, release for sale, and use of certain harmful substances and preparations. It is thus possible to introduce a limit for a certain substance used in medicinal products. However, in practice it is not probable that this would be done, as Reach is piece of general legislation and not adapted to such a specially regulated field as medicinal products. Nor would Reach entail the registration of data about the use of medicinal products, as human and veterinary medicinal products are exempted from the registration requirement.

On the other hand, inspiration can be found for the creation of new EU legislation from the process for identifying substances for new limits and substances that may not be used without authorization. For instance, Reach has a list available on the home page of the European Chemicals Authority called the candidate list. On the basis of this list a number of substances placed on the list are prioritized in Reach for authorization assessment. Reach has a specially delineated process for how new substances are placed on the candidate list. Such a public list can function as a kind of *Nota Bene* list.

of substances that are being singled out for special monitoring, which sends a signal to
the industry regarding what substances are in the pipeline and have been deemed to
warrant special attention. When it comes to new limits in Reach, initiatives for such
limits can be taken both by the European Chemicals Authority and by a Member State,
which composes a so-called limits file whose contents are specified by Reach. This,
too, is a process that can serve as a model when new legislation is drafted. It can be
important that individual Member Countries are allowed to take the initiative for
placing a certain substance in the legislation.

A primary purpose of Reach is to generate data about substances. The registration
obligation establishes a responsibility for producers and importers to gather existing
data and create new data, on the basis of certain testing methods established under the
Commission’s Regulation (EC) No. 440/2008 on testing methods according to Reach.
The amount of data is determined by what amount of the substance is produced or
imported annually. All registrations are done electronically to the European Chemicals
Authority (ECHA). All registrations, including all data, are found in a searchable
database, Reach-IT. The electronic tool is called UCLID 5. Ultimately it is intended
that data coming in in connection with assessment of pesticides, which involves a
procedure similar to that for assessing medicinal products, will be included in
UCLID 5.

A searchable database is often necessary to winnow out substances that cause
particular concern. It may therefore be necessary also in the field of medicinal products
to consider how data from active substances in medicinal products should be collected
for use to single out those medicinal substances that need to be addressed. One avenue
would be a database at the European Medicines Agency, EMA, similar to the one
under Reach.

On the whole, Reach can probably not deal with the problem of emissions of medicinal
substances into the environment in an adequate manner. The conclusion of the
workgroup is that these issues are best addressed within the regulatory system for
medicinal products. On the other hand, Reach has many processes that can be used as a
model when the regulatory system for medicinal products is revised. Examples of this
are the establishment of a candidate list and the fact that an individual Member
Country can take the initiative for limits. A further model could be the searchable
database that was set up for Reach.
3 National experience and new initiatives

At the national level there is experience with generating environmental data and applying data via environmental classification of medicinal products and procurement criteria for medicinal products that can be brought to bear as a point of departure and platform for drafting a proposal for changes in medicinal products legislation in order to place environmental requirements on the production of medicinal products.

3.1 Findings from previous governmental commissions

The Medical Products Agency was commissioned by the government in December 2002 to investigate the environmental impact of medicinal products and cosmetic and hygiene products, including packaging. The commission included a risk assessment for environmental impact on the basis of prevalence in the environment in relation to current sales volume. Moreover, the commission included the drafting of a proposed measures to reduce the environmental impact from these product groups and to study how information on quantities and content of substances in the product groups could be improved and made more readily accessible. Also included was an investigation of the possibility of introducing environmental classification of medicinal products. The commission submitted its report in August 2004.14

Of the c. 1,200 active medicinal substances found on the Swedish market, the assessment was limited to 27 substances. The selection of substances was done by weighing data for degradability/half-life times, data collected from the medicinal products industry, and data published in the literature, as well as information on recorded concentrations in the environment and current Swedish sales statistics. As a result, it emerged that the sex hormones oestradiol and ethinyloestradiol posed a risk of impacting the water environment.

Assessments of environmental hazardousness without consideration of sales volume or concentrations in the environment were carried out in accordance with the regulations of the Swedish Chemicals Agency for classifying and labelling chemical products. The tests that form the basis for environmental hazardousness comprise so-called short-term or acute toxicity, biological degradability, and bioaccumulation capacity. Among the substances for which there were sufficient data to enable an assessment of environmental hazardousness, nine substances were classified as hazardous to the water environment. They were diklofenak, ethinyloestadiol, ibuprofen, ivermektin, metoprolol, norethisterone, oxitetracycline, paracetamol, and tylosin. The remaining substances were not regarded as posing any acute risk for the water environment, but here uncertainties remain regarding long-term environmental risks. Long-term toxic effects occur in certain cases at the concentrations actually measured in the environment.

In the report the Medical Products Agency pointed out that measures to reduce the potential impact of medicinal products on the environment must be grounded in knowledge about above all long-term effects, which was lacking for most authorized medicinal substances. Greater consideration for the environment in European medicinal products legislation was also regarded as necessary. After the report EU guidelines for assessing environmental risks were revised, and stricter requirements for assessments of degradability, bioaccumulation, and long-term effects were introduced. Sweden played an important role in the reworking of these guidelines.\(^{15}\)

In summary, work with the report revealed that lack of data was a problem. For most medicinal products there was so little environmental data that it was difficult to estimate the concentration at which a risk of negative environmental impact in the water environment might arise.

### 3.2 Environmental classification of medicinal products amasses knowledge

The Medical Products Agency report from 2004 investigated the possibility of classifying medicinal products on the basis of a scientific evaluation of their effects on the external environment. The relationship with current EC law and various classification models was illuminated. Two measures for future environmental classification were proposed:

- The government and competent authorities should work to bring about a discussion at the Community level of a European environmental classification system for medicinal products.
- In anticipation of a possible European environmental classification system a voluntary national system can be introduced.

The Medical Products Agency also pointed out in the report that classification could have some effect if it was regarded as a knowledge base in public procurement. Both the Commission and the European Court of Justice have accepted that attention may be paid to environmental criteria in public procurement.

#### 3.2.1 The Swedish classification system for medicinal products

The association of the Research-based Pharmaceutical Industry in Sweden (LIF) took hold of the issue of classifying and, soon after the Medical Products Agency report came out, took the initiative for national environmental classification of medicinal products along the lines of what was presented in the report. The model was developed in collaboration with Apoteket AB, the Medical Products Agency, and the Stockholm County Council as well as Sweden’s Municipalities and County Councils. The goal was to have a section on environmental impact for all active substances at [www.fass.se](http://www.fass.se) by 2011.

The Swedish classification model has been described and/or evaluated in several studies.\(^{16}\) At present all groups of medicinal products (ATC) have been gone through,
and information is available at http://www.fass.se/LIF/miljo/miljoinfo.jsp for all products that have been assessed. Now continual three-year updates of sales data are done, along with reviews of incoming new data.

3.3 **Procurement criteria for medicinal products**

At many county councils the results of the environmental classification are factored into the recommendation work of their medical products committees, partly at the initiative of the Collegium of Medical Products Committee Chairs (LOK). In the long term, this classification can thus lead to a shift in pharmaceutical prescriptions and consumption in the direction of more environmentally adapted medicinal products. It is hoped that this will thereby prompt producers of medicinal products to try to make new products they develop less of a burden to the environment than at present. To further stimulate producers in this direction, environmental classification of medicinal products should be made internationally accepted and used.17 This was also something that participants at the 2009 Swedish Presidency Meeting on Sustainable Development for Medicinal Products endorsed.

Criteria have been developed within the framework of the Swedish Environmental Management Council’s activity in a project with the association of the Research-based Pharmaceutical Industry (LIF), the Generika companies, Stockholm County Council, the Western Götaland Region, Uppsala County Council, Blekinge County Council, and the Medical Products Agency as participating partners. In 2010 the project group discussed a long-term strategy for criteria work, and the first target was reached on 21 December 2010 when the board of the Swedish Environmental Management Council adopted criteria for procurement criteria for pharmaceuticals and their packaging following comprehensive circulation for comment.

Procurement criteria for pharmaceuticals and their packaging (2011-01-21, version 4.0) has now been published at http://www.msr.se/kriterier/lakemedel and treats emissions from manufacturing, content of environmentally hazardous substances, and the risk of poor working conditions in the production phase. Suppliers undertake at the start of a contract to provide their own environmental information for the products to be covered by the contract or to refer to other environmental information corresponding to the transparent model for environmental classification18 of medicinal products collaboratively developed by LIF, the Medical Products Agency, Apoteket AB, Sweden’s Municipalities and County Councils, and Stockholm County Council. This means among other things that before environmental information is published, it must be reviewed and authorized by an independent third-party expert, whereupon the suppliers undertake to upload this information at www.fass.se or on some other freely accessible Web site.

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3.4 Risk assessment of emissions of active substances from production

The pharmaceutical industry’s environmental committee pointed to AstraZeneca’s ongoing work as relevant to the continued discussions to introduce environmental considerations in production. AstraZeneca is methodically working to ensure that emissions from its production units do no harm to the immediate environment. This work is part of a global strategy for safety, health, and the environment that top management at the company has adopted. As a key component in environmental work, AstraZeneca has developed the concept of Environmental Reference Concentration (ERC). ERC is the concentration of an active medicinal product substance in water that is not expected to cause harmful effects on aquatic organisms, animals, or humans. The strategy for safety, health, and the environment comprises both the company’s own production facilities and production run by suppliers. AstraZeneca is now actively working to implement the use of ERC and thus ensure risk management of emissions of medicinal products in production both inside and outside the company.

AstraZeneca is developing ERCs for individual medicinal products. These are determined on the basis of current scientific knowledge about the potential risks for each medicinal product substance, as well as the guidelines that are in place for risk assessment of chemicals. On this basis, emissions of medicinal substances in treated streams are assessed and whether they pose a risk to the environment. AstraZeneca has currently determined the ERC for more than 30 of its most important medicinal substances, and work continues to ascertain the ERC for further medicinal substances.

Through a combination of good knowledge of the production process, analysis of emissions, and what happens with emissions after they leave the facility, ERC can be used to carry out site-specific risk assessment of emissions. AstraZeneca has recently submitted an article to a scientific journal with a detailed description of how ERC is determined.

3.5 Collaboration for improved purification methods in India

India accounts for a major share of world production of medicinal products. To meet today’s and tomorrow’s requirements in the medicinal products industry, the Swedish Environmental Research Institute (IVL), in collaboration with the Medical Products Agency, is actively working in India to develop and implement environmental technology solutions. During the autumn of 2011 IVL and the Medical Products Agency will jointly engage the Indian medicinal products industry in discussions to devise a strategy for implementing sustainable environmental technological solutions that will satisfy future environmental requirements within the EU. The plan is also to initiate full-scale production as demonstration facilities in order to proactively highlight the possibility of implementing modern environmental technology for all production of medicinal products in India.
4 Proposal for regulating environmental consideration in production of medicinal products

4.1 Disparate goals in environmental and medical products legislation

Whereas environmental legislation is clearly informed by the goal of sustainable development, the goal for medicinal products legislation is for medicinal products to be safe and to have the intended therapeutic functions. At the same time, good health is a central target subsumed under the goal of sustainable development. The objective of sustainable development is a long-term one – good conditions for all current and coming generations. The objective of medicinal products legislation can largely be said to focus more on the short term, as it primarily concentrates on the perspective of the individual and not the goal of sustainable development for all people. One example is the risk of developing antibiotic resistant bacteria, partly as a result of extensive and often reckless prescriptive use and partly as a consequence of emissions of medicinal products residues, which may be a risk factor. Nor from a strictly business perspective can production emissions be regarded as either sustainable or defensible.

Medical products legislation does not sufficiently rest on the objective of sustainable development, even though this goal is inscribed in Article 3 in the Treaty on European Union (formerly Art. 2 EC Treaty), in the Swedish Instrument of Government, and the portal paragraph of the Environmental Code. Good health, including access to functioning medicinal products that are properly used, is part of sustainable development.

The goal of medicinal products legislation must also be to create equity between generations, e.g. by ensuring that people in the future will have access to effective medicinal products and to pure drinking water without residues from medicinal products. The responsibility for this is shared by present and coming generations, but it is only those who are living at the time who can work towards it. From a precautionary point of view, it is urgent to take action. However, Sweden cannot act alone, on the one hand because Swedish medicinal products legislation is harmonized with EU law and, on the other hand, because production often takes place in countries other than those in which the medicinal products are used.

To partially amend the goal formulation for an entire legal field within the EU takes a long time and may encounter resistance. At the same time it must be underscored that sustainable development is one of the fundamental pillars of the EU.

In light of the fact that the basic legal documents from the EU in the field of medicinal products law were adopted under Art. 95 in the EC Treaty (now Art. 114 in the Treaty on the Functioning of the European Union,19 TFEU), where the objective is to create a harmonized market for, in this case, medicinal products, Member States are not

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19 EUT C 115, 9.5.2008 p. 47.
permitted to impose their own regulations to protect the environment, except in emergencies (EC Treaty Art. 95(10), now Art. 114(10) TFEU).

The formal procedure for amending (in this case) the regulation of medicinal products was previously stipulated in Art. 95(8) of the EC Treaty, now corresponding to Art. 114(8) TFEU, in which it is stated that when a Member State raises a specific problem on public health in a field which has been the subject of prior harmonization measures, it shall bring it to the attention of the Commission which shall immediately examine whether to propose appropriate measures to the Council. As was mentioned in the introduction, antibiotic resistance, which can arise as a result of incautious use of medicinal products and potentially of emissions in connection with production, is an instance of such a public health problem.

Work at the EU level is necessary to create an understanding for why this amendment of the goal formulation of medicinal products legislation is needed. In an EU context environmental issues relating to the field of medicinal products have not received high priority, which has been shown, for example, by previous Council negotiations and is also confirmed in present efforts. This runs counter to Article 11 TFEU, which declares that environmental consideration must be integrated into all policy areas. It is therefore particularly gratifying that the Commission, in its Communication on a Renewed Vision for the Pharmaceutical Sector, COM (2008) 666 Final, includes environmental consequences. The Commission declares that what is now needed is a focus on measures that can reduce potentially harmful consequences of medicinal products for the environment and public health, which is also reflected the objectives they set up. The proposal also enjoys the endorsement of several stakeholders, including LIF, SKL, SLL. At the Medical Product Agency’s Presidency Conference on Sustainable Development and Pharmaceuticals in November 2009, various stakeholders presented their views on future developments in the perspective of this proposal. The conference participants were unanimous that medicinal products in the environment pose a problem, and the high concentrations of medicinal substances in drinking water and groundwater in India were put forward as an example. The Commission clarified that its priority regarding medicinal products and sustainable development lies in the areas of antibiotic resistance, hormone-disruptive substances, and the impact on people of the aggregate mixture of various chemicals, including medicinal products.

One distinct objective should be to reduce the total consumption of medicinal products, e.g. antibiotics, when there are alternative forms of treatment. There are also ethical considerations to be factored in. It must not be perceived that the health of the present generation or of individuals is being sacrificed for the benefit of coming generations.

4.2 Deficiencies in environmental consideration in medicinal products legislation

According to current legislation on medicinal products, an environmental risk assessment, among other things, must be submitted with applications for authorization of a medicinal product. However, one problem is that for a medicinal product for humans, environmental risks can never be factored into the risk/benefit assessment, and an application can therefore never be rejected on this ground. Nor is therefore any scope to accept risks in relation to benefits with different types of medicinal products in the particular assessment, e.g. cancer medication and pain-relieving medication or a medicinal product like nicotine strips. On the other hand, in the benefit/risk assessment
of a veterinary medicinal product, any risk of undesirable environmental effects in the use of the medicinal product may be borne in mind when the decision is made whether to authorize the medicinal product, although this does not include environmental effects relating to production. Environmental risks relating to the actual production of the medicinal product cannot either constitute a ground to revoke authorization.

Requirements that may be imposed on production regarding good manufacturing practice (GMP) are intended to establish and guarantee that the medicinal product is qualitatively assured and manufactured in a safe manner. Because legislation on medicinal products is harmonized, individual Member Countries are not permitted to impose their own regulations in the field. For instance, the Medical Products Agency established in 2004 that it is not compatible with EU law to impose binding national requirements for the introduction of environmental classification systems. Thus all amendments to legislation on medicinal products regarding the authorization process require amendments at the EU level.

Regarding the matter of whether medicinal products legislation should address environmental problems that may arise from production, there are various alternative avenues for action, see the Medical Products Agency’s 16 December 2009 report on the government’s commission regarding the possibility of tightening environmental requirements for the production of medicinal products and active substances.

If consideration could be given to the environmental situation in the production of medicinal products, within the framework of the rules and guidelines for good manufacturing practice, this would apply not only to medicinal products manufacturing in the EU/EEA. This is because producers or importers of medicinal products within the EU/EEA are obligated to see to it that all production processes are carried out in accordance with good manufacturing practice and, respectively, to ensure that imported medicinal products have been produced observing the norms of good manufacturing practice that are at least equivalent to those adopted by the Community. These obligations apply regardless of where some production of a medicinal product takes place, as long as the production or the importation occurs within/into the EU/EEA.

If changes in medicinal products legislation are to be considered, this would entail that the European Medicines Agency, EMA, must give priority to the issue of the environmental impact of medicinal products and place it on the agenda. It also means that the Commission also needs to put forward a proposal designed, on the one hand, to revise the foundations of medicinal products legislation in accordance with what has been presented and, on the other hand, to develop effective regulations in which the environment is also placed in focus. However, there is nothing to stop individual Member Countries from taking the first initiative. Under Art. 114(8) TFEU the Commission is obligated to immediately examine whether to propose appropriate measures to the Council when an individual Member Country raises an issue regarding public health in a field subject to prior harmonization measures.

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4.3 Proposed changes in medicinal products legislation in the EU

4.3.1 Environmental requirements for manufacturing medicinal products

The proposal put forward in this report is intended to achieve regulation that enables the control of emissions into the environment of substances stemming from pharmaceutical manufacturing whose discharge it is especially urgent to reduce. The intention is also to attempt to ensure that this regulation has the greatest possible impact.

Against this background we have found it most appropriate to propose regulations for environmental control within medicinal products legislation, within the framework of good manufacturing practice, GMP. What is unique about the already existing regulations on manufacturing and GMP is that they also impact third countries in that manufacturers wishing to export medicinal products into the EU are obligated to comply with regulations for production that apply within the EU. By adding regulations on environmental control among production regulations, they have an impact on third countries as well.

When new requirements for control are introduced, it is also important that they be complied with. Monitoring must be undertaken so that violations are discovered and can be addressed. A further advantage of placing environmental requirements in the framework of GMP is that there is a well-developed and well-functioning inspection system for monitoring production and GMP. The competent authorities have both the right and the obligation to carry out inspections to see, among other things, whether GMP is complied with by manufacturers. By placing environmental requirements in the framework for GMP, inspection rules will also apply to monitoring that environmental requirements are observed. Thus no new such system needs to be constructed.

4.3.2 The proposal and why it looks the way it does

As was described in Section 2.2.3 there are comprehensive rules about what is required for authorization to manufacture medicinal products in both of the medicinal products directives. One of the requirements is that manufacturers must follow GMP in the production both of active substances and of parts of or whole medicinal products. The Commission has been delegated the power to adopt directives in regard to indicating what good manufacturing practice entails. The Commission has also adopted two such directives: one for human medicinal products and one for veterinary medicinal products, see Section 2.2.3.1. For good manufacturing practice in the production of active substances used as starting materials, the Commission has adopted guidelines in accordance with the authorizations in the medicinal products directives.

A key question in this connection is where a new requirement regarding environmental control within GMP should be placed. The directives on GMP are Commission directives. This means that the Commission has adopted acts using powers granted in the medicinal products directives. According to the Treaty on the Functioning of the European Union (TFEU) the Commission may adopt acts of general application that are not legislative documents and that supplement or amend certain non-essential elements of the legislative document, see Art. 290 in the Treaty. What is proposed now,
the addition of a new field of control – intended to safeguard both public health and the environment – in the manufacturing of medicinal products, would be to extenuate such authority too far. To attain the purpose of the proposal for environmental control, changes in directives 2001/82/EC and 2001/83/EC must be proposed.

The medicinal products directives are directives whose primary purpose is to safeguard public health and to do so without hampering the development of medicinal products or trade with medicinal products within the Community, see introductory points 2 and 3 in the two directives. The environmental control proposed in this report is intended to protect both public health and the environment. In order not to revise the medicinal products directives too much regarding the purpose of the legislation, it is proposed that the detailed rules for environmental control be placed in a legal document other than the medicinal products directives.

The proposal is therefore to insert into the medicinal products directives an obligation for manufacturers of medicinal products to comply with the requirements in a legal document in which emission levels for certain substances are stipulated. This obligation should be inserted into the medicinal products directives in the requirement to live up to GMP in production. A special legal document in which emission levels are stipulated must also be adopted, see Figure Z1. As was made apparent in Section 2.3 about the EU’s environmental legislation, there is no existing legal document that suits this purpose.

The point of departure for the proposal of a new legal document is to state in this document what medicinal substances need to be controlled as well as the emission levels of these substances that are not permissible for the environment. To achieve a rapid impact, a new regulation is preferable, as it would become directly applicable in all Member States and would not need to be implemented in national legislation. To find a good structure one might look at how cosmetics legislation within the EU is constructed. For cosmetics, a new regulation was recently adopted by the European Parliament and Council, (EC) No. 1223/2009. This regulation contains annexes in which substances are listed that are prohibited for use in cosmetic products or in which limits for use of these substances are established. The Commission was delegated the power to adopt changes in the annexes. A similar set-up would entail several advantages: emission limits would apply throughout the EU; they would have the same structure in all Member States; and changes would be less complicated to implement in that the Commission could adopt them.

4.3.3 Concrete proposals for changes in medicinal products legislation

4.3.3.1 Definition of GMP

As GMP legislation is constructed at present, the medicinal products directives stipulate that GMP must be complied with in the production of medicinal products, and the Commission’s directive defines the concept of good manufacturing practice and establishes principles and guidelines for GMP. We propose that the definition of GMP be taken from the Commission’s directive and be inserted into Art. 1 in the respective medicinal products directives. In both medicinal products directives Art. 1 comprises multiple definitions.

We also propose that the definition be expanded to require that the new legal document with emission levels for certain substances must be followed when controlled substances are involved in production. If the definition is moved to the medicinal
products directives and also states that the requirements in the new regulation must be complied with, the purpose of including environmental control in GMP will be achieved. The intention of the proposal is for environmental requirements to apply also to the production of active substances.

In that the new legal document covers the emission of certain specially listed substances, only those manufacturers that actually deal with these substances will be affected by the new requirements. These producers must show that they satisfy the emission requirements in the new regulation in order to be granted authorization to manufacture medicinal products, and they must of course comply with the requirements in the new regulation also after their authorization has been assessed. If the proposal is implemented, this will be monitored within the framework of the inspections the competent authorities both can and must carry out under already existing rules about inspection of producers.

Proposed wording (new text in bold):

good manufacturing practice is a component of the quality assurance that is intended to make sure that the products are always produced and monitored in such a manner that they satisfy quality requirements that are appropriate for their intended use as well as the requirements established in “the legal document.”

4.3.3.2. The power to revoke authorization for manufacturing

To be able to perform effective monitoring, a competent authority should be able to take action if it is revealed that a manufacturer is no longer complying with environmental requirements. As the medicinal products directives are formulated today, manufacturing authorization may be suspended temporarily or revoked if something occurs or if something is revealed after the authorization was granted that entails that GMP is no longer being complied with, Arts. 85.2 and 118.2, respectively. This regulation should also include the circumstance of environmental requirements not being complied with in accordance with our proposal, as they are part of the GMP definition. For the sake of clarity, consideration should nevertheless be given to the possibility of also inserting here an express reference to the fact that these measures may be taken also if the requirements in the new legal document are not complied with.

Proposed wording for Art. 85.2 in Directive 2001/82/EC (new text in bold)

The competent authority of a Member State may, in addition to the measures provided for in Article 84, either suspend manufacture or imports of veterinary medicinal products from third countries or suspend or withdraw the manufacturing authorization for a category of preparations or for all preparations in the event of non-compliance with the provisions regarding manufacture or imports from third countries. This also applies when the requirements in (legal document) are not satisfied in the manufacture of medicinal products containing some substance encompassed by (legal document).

Proposed wording for Art. 118.2 in Directive 2001/83/EC (new text in bold)

In addition to the measures specified in Article 117, the competent authority may suspend manufacture or imports of medicinal products coming from third countries, or suspend or revoke the manufacturing authorization for a category of preparations or all preparations where Articles 42, 46, 51 and 112 are not complied with. This also applies when the requirements in (legal document) are not satisfied in the manufacture of medicinal products containing some substance encompassed by (legal document).
4.3.3.3. Articles with documentation requirements for application for authorization of medicinal products

The proposed change regarding GMP will entail stricter requirements for those who manufacture medicinal products. To attain a wall-to-wall system for how medicinal products control is structured certain new requirements should be imposed on those applying for authorization to market medicinal products. Additions should be made in Article 12.3 in Directive 2001/82/EC and in Art. 8.3 in Directive 2001/83/EC. This should be done to obligate anyone wishing to have a medicinal product authorized for marketing to submit with the application documents showing that the producer(s) the applicant uses comply with environmental requirements. The documentation requirement will also apply to anyone applying for authorization to market a medicinal product manufactured by the applicant. Through such regulation it will also be possible to reject an application for authorization to market a medicinal product if the environmental requirements for manufacturing are not complied with (Art. 30 first paragraph Directive 2001/82/EC and Art. 26.2 Directive 2001/83/EC, respectively).

The document proposed as necessary below can consist of an inspection protocol set up in connection with an environmental inspection at a production site carried out under Arts. 80 and 111, respectively.

Proposed wording for Art. 12.3 in Directive 2001/82/EC (new text in bold)

The application for marketing authorization shall include all the administrative information and scientific documentation necessary for demonstrating the quality, safety and efficacy of the veterinary medicinal product in question. The file shall be submitted in accordance with Annex I and shall contain, in particular, the following information:

m) a document showing that the manufacturer is authorized in his own country to produce veterinary medicinal products and, when the application regards medicinal products containing a substance listed in the annex to (legal document), documents showing that the manufacturer or manufacturer of the active substance complies with the requirements in (legal document).

Proposed wording for Art. 8.3 in Directive 2001/83/EC (new text in bold)

The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:

k) a document showing that the manufacturer is authorized in his own country to produce medicinal products and, when the application regards medicinal products containing a substance listed in the annex to (legal document), documents showing that the manufacturer or manufacturer of the active substance complies with the requirements in (legal document).

4.3.3.4. The new legal document

As it is the Commission’s prerogative to propose new legal documents, and owing to the relatively short time allotted in the government’s commission, no structure for the new legal document is proposed here.

A key component of the structure of this document is to establish a procedure for setting up emission limits for the substances to be regulated. It may require a body within EU, or under EMA, that possesses the environmental competence to receive and deal with documentation and questions surrounding the investigation of substances that should be controlled and for setting up reasonable emission levels for them. As stated above, the candidate list developed within Reach could be something to start out with...
in considering how new substances that need to be controlled should be captured and dealt with. Bearing in mind that medicinal products can be of life-and-death importance to people, it should also be possible to apply for and be granted exemption from emission limits in particular cases where the benefit of manufacturing exceeds the negative environmental impact the manufacturing entails. This, too, should be regulated in the new legal document.

Figure Z1. GMP in EU legislation according to the proposal in the report.

4.3.3.5. The new Directive on Counterfeit Medicinal Products

The new Directive on Counterfeit Medicinal Products, see Section 2.2.6, contains, among other things, amendments to articles in the Directive on Human Medicinal Products 2001/83/EC that are included in the proposals presented in this report. Art. 8.3 with documentation requirements for applications will include a requirement for confirmation by the applicant that the manufacturer has ascertained that the producer of the active substance complies with GMP for the active substance. This does not affect the proposed amendment to Art. 8.3 put forward above but rather strengthens the control of compliance with the new environmental requirements on the part of the producer.

Article 46 f is expanded with a requirement that anyone holding authorization for manufacturing must have control of his suppliers in regard to their compliance with GMP for active substances. Several of the changes in the Directive on Counterfeit Medicinal Products strengthen requirements that manufacturing of active substances must comply with GMP. Among other things, in the amending Directive the Commission is authorized to regulate GMP for active substances through delegated documents. This differs from the current Directive where the Commission is charged with adopting detailed guidelines for GMP for active substances. It will be important, in these new delegated documents, also to insert a clarification that the environmental requirements stated in the medicinal products directives’ definition of GMP also apply to the manufacture of active substances, as proposed in this report.

4.3.3.6. Using existing knowledge in creating the new legal document

The knowledge we have of medicinal products and their impact on the environment comes exclusively from research, e.g. through the research foundation MistraPharma and from companies applying for authorization of their products. Environmental data
generated today in connection with the authorization of a medicinal product is gathered within the framework of the medicinal products directives, which e.g. regulate what documentation the company needs to present to be granted marketing authorization (see Sections 2.2.4.3 and 2.2.4.4.). The proposals in this report target the manufacture of medicinal products, for which there are no requirements regarding environmental data today. The EU Commission’s conclusions and research within MistraPHarma indicate that priority should be given to antibiotics and hormone-disruptive substances as well as substances that can pose a risk to the environment because they are used and manufactured in large volumes. Regarding antibiotics and their risk of causing resistance, it is important to point out that this is also a global priority for the UN. Further research in the field is receiving high priority, and as our knowledge advances it will also be possible to identify other substances for regulation.

In the future, in order to enable priorities to be set and limits determined for medicinal products that should not be released into the environment, more comprehensive information will be needed about the properties of substances. Neither the Medical Products Agency nor EMA currently has an environmental database in which it is easy to access information on active medicinal substances. Such a database would facilitate the updating of priorities and setting relevant limits based on the environmentally toxic properties of substances (PNEC). Experience from Reach should be brought to bear, and data published by FASS.se should also be considered when limits are set. However, this is predicated on these data being fully accepted by the European authorities. FASS.se environmental data are based on voluntary participation and have not been reviewed or authorized by any medicinal products authority, and there is moreover the problem of lack of data for certain substances. On the plus side, participants at Sweden’s 2009 Presidency Meeting on Sustainable Development expressed their support for the introduction of environmental classification at the EU level. This is a matter that should be discussed further in EU work, along with in what way already available environmental data can be used in support of limiting environmental risks in the manufacture of medicinal products.

Requiring control and documentation of concentrations in the outflowing wastewater for all active substances produced at a facility appears to be a natural step, as in many cases suitable methods of analysis are already available or should be developed.

Consideration can be given to setting a general limit for emission of active substances in the water environment in production corresponding to the one for authorizing medicinal products today, 0.01 µg/L, when the availability of environmental data is so deficient that no substance-specific limit can be determined with sufficient certainty.

In summary, substance groups have been identified that should find acceptance as the first substances to be regulated in the proposed legislation – antibiotics and hormone-disruptive substances as well as substances that pose a risk to the environment owing to the large volumes that are produced and used. As our knowledge advances, other substances or groups of substances may be slated for regulation. A system for how this can be carried out should be developed at the EU level.

4.4 Trade and sustainable development

As mentioned, sustainable development is an overarching goal for all policy areas in both national and international work. This means that our international system of trade must take into consideration the three dimensions of sustainable development, that is, include economic, social, and environmental aspects.
Production of medicinal products in low-cost countries contributes to job opportunities and the transfer of knowledge between countries, for example, as well as cheaper medicines in Sweden. However, it can be questioned whether this is happening in harmony with the goal of sustainable development. One example that points up insufficiencies in achieving the goal of sustainable development is the spread of antibiotic-resistant bacteria as a result of emissions from manufacturing. The EU and WHO rank the rapid development of resistance to antibiotics as one of the three greatest threats to human health. This resistance means that one of humanity’s most vital medicines, antibiotics, may become ineffective. The lack of effective antibiotics complicates and delays treatment of commonly occurring infections both in outpatient care and in hospitals. Increased mortality, extended care periods, and higher care costs represent a heavy burden on the already strained economy of healthcare.

Among other things, our proposal aims to come to grips with parts of this global problem. More in-depth analyses are of course needed, but this is not part of the commission at hand.
5 Conclusions and proposed measures

Global public health is negatively impacted by the emission at unacceptable levels of pharmaceutical substances from production, above all in developing countries. To achieve sustainable development for pharmaceutical manufacturing, in which ecological, economic, and social development are in harmony, legal and voluntary measures must be taken to ensure more responsible pharmaceutical production in all its steps.

The proposal put forward in this report is intended to achieve regulation that enables the control of emissions into the environment of substances stemming from pharmaceutical manufacturing whose discharge it is especially urgent to reduce. The intention is also to attempt to ensure that this regulation has the greatest possible impact.

In this report commissioned by the government, the Medical Products Agency presents proposed regulations for environmental control within medicinal products legislation, within the framework of Good Manufacturing Practice, GMP. What is unique about existing regulations regarding production and GMP is that they also impact third countries, as manufacturers wishing to export medicinal products to the EU are obligated to comply with regulations for production that apply in the EU. By also placing rules for environmental control among manufacturing regulations, they also have an impact on third countries.

When new control requirements are introduced, it is important that they also be complied with. Monitoring must be pursued in order to uncover violations and take measures. A further advantage of placing environmental requirements within the framework of GMP is that there is a well-developed and well-functioning inspection system for monitoring manufacturing and GMP. The competent authorities have both the right and the obligation to carry out inspections to check, for example, how producers observe GMP. By placing environmental requirements within the framework of GMP, inspection protocols will also apply to the monitoring of compliance with environmental regulations. Thus no new system need be set up; all that is needed is the addition of internal or external environmental expertise.

The long-term objective should be to introduce the EU’s GMP environmental regulations at the global level. At present GMP is highly harmonized. The requirements that can be stipulated in accordance with GMP today are not only harmonized within the EU, but also between the EU and the Pharmaceutical Inspection Co-operation Scheme (PIC/S), an affiliation of currently 39 medical products agencies throughout the world. There is also an exchange of information with WHO, which is the third major actor with its own global GMP network.

To gain acceptance for the need to implement the proposed changes, what is required at the EU level is an understanding of connection between health and environmental issues. Moreover, the matter must also be politically anchored in Member Countries. This is especially true of the much-discussed environmental problems related to the production of medicinal substances in the Third World.
To achieve a regulation of emissions from pharmaceutical manufacturing that impacts public health, including the external environment, the Medical Products Agency proposes the following:

1. **Changes in medicinal products directives**

   In the medicinal products directives, insert an obligation for manufacturers of medicinal products to comply with the requirements of a special new legal document, a new EU regulation (see item 2 below), in which emission levels for certain substances are stated. The new obligation in the medicinal products directives should be inserted in the requirement to comply with GMP in production.

   **Rationale:** Today EU medicinal products legislation and environmental legislation do not comprehend environmental requirements for pharmaceutical production regarding emission of medicinal substances. The government has requested a platform on which to implement a change in GMP legislation at the EU level for the purpose of introducing environmental considerations in production. A key question in this connection is where new requirements regarding environmental control in GMP should be placed. The directives for GMP are Commission directives. This means that the Commission has adopted documents on the strength of authorizations in medicinal products directives. What is now being proposed, the addition of a new control area for purposes of both public health and environmental protection in medicinal products production, would be to extend such authorization too far. To realize the intentions of the proposal regarding environmental control, changes in directives 2001/82/EC and 2001/83/EC must therefore be proposed.

   The medicinal products directives are directives whose primary purpose is to safeguard public health and to do so without hampering the development of medicinal products or trade in medicinal products within the EU. The environmental control being proposed is designed to protect both public health and the environment. In order to avoid revising the medicinal products directives too much regarding the purpose of the legislation, it is therefore proposed that the detailed rules for environmental control be placed in a legal document other than the medicinal products directives.

   The proposal is thus to insert in the medicinal products directives an obligation for producers of medicinal products to comply with the requirements in a legal document in which emission levels for certain substances are stated. This obligation is placed in the medicinal products directives in the requirement to comply with GMP in production. A special legal document stating emission levels must also be adopted, as there is no other legal document in EU environmental legislation that is suitable for this purpose.

2. **Introduction of a new EU regulation**

   A new EU regulation should be created. The point of departure in proposing a new legal document is that it should stipulate the medicinal substances that need to be controlled in terms of emissions from production as well as the emission levels that are not permissible. Cosmetics legislation in the EU might serve as a model for structuring this document.

   **Rationale:** To achieve a rapid impact, a new regulation is preferable because it would come directly into force in all Member Countries and need not be implemented in national legislation. For cosmetics, a regulation was recently adopted by the European Parliament, (EC) No. 1223/2009. The regulation contains annexes where, among other things, substances are listed that are prohibited for use in cosmetic products or for
which limitations are laid down regarding their use. The power to adopt changes in the
annexes was delegated to the Commission. An equivalent set-up in itself would entail
multiple advantages: emission limits apply to the entire EU, they have the same
structure in all Member States, and changes are less complicated to effect in that the
Commission can make them.

3. Proposed substances for priority attention
What should receive top priority for a first step in the above-mentioned EU regulation
are those pharmaceutical substances for which there is scientific evidence that the
external environment, and thereby public health, is negatively impacted. First and
foremost this concerns antibiotics, certain medicinal products with hormone-disrupting
substances, and substances that may constitute a risk to the environment in that they
are used and produced in large volumes.

Rationale: EU and WHO rank the rapid development of antibiotic resistance as one of
the three greatest threats to the health of individuals.

What should receive top priority in a first step in the above-mentioned EU regulation
are those pharmaceutical substances for which there is scientific evidence that the
external environment, and thereby public health, is negatively impacted. First and
foremost this concerns antibiotics, certain medicinal products with hormone-disrupting
substances, and substances that may constitute a risk to the environment in that they
are used and produced in large volumes.

The knowledge we have about medicinal products and their impact on the environment
comes exclusively from research through e.g. the research foundation MistraPharma
and from companies applying for authorization of their products. Findings from
previous investigations indicate clear gaps in our knowledge, which makes it difficult
to make a fair selection of environmentally hazardous substances and to establish
relevant concentration limits for emissions. However, the EU Commission’s
conclusions in environmental work with medicinal products, and research within
MistraPharma, indicate that substances that can cause antibiotic resistance, medicinal
products with hormone-disrupting substances, and substances that are used in very
large volumes should receive top priority.

The work that most clearly touches on medicinal products emissions into the water
environment today is the EU directive establishing a framework for Community action
in the field of water policy. On a list of proposed priority substances, that is, substances
that constitute a significant risk to the water environment, there are four medicinal
substances. Two hormones, 17 beta oestradiol, a natural oestrogen produced by
humans and animals, and 17 alpha ethinyloestradiol, a synthetic oestrogen used
in contraceptives and other types of hormone treatment, along with two anti-
inflammatory medicinal substances, diklofenak and ibuprofen.

4. Work to identify further candidates
The new EU regulation should establish a procedure for how to identify further
substances and how to determine concentration limits. These tasks will need to be
addressed by some EU body that has the relevant environmental expertise.

Rationale: The report presents no detailed proposal for how this procedure should be
set up. What substances should be regulated, other than those mentioned under item 3
above, is not clear at present. This prioritization should be done at the EU level in
cooperation with Member States. At present it is difficult to identify any existing body within the EU that has the pharmaceutical expertise and environmental expertise to carry out these assignments. The principal responsibility should lie with the pharmaceutical authority EMA, with some form of cooperation between EMA and the EU chemicals authority, ECHA, as a possibility. This EU body should also work closely with research and other stakeholders. The report provides a broad compilation of examples of experience from other EU regulation in the environmental area, voluntary industry initiatives, research, and previous governmental commissions performed by the Medical Products Agency that may be of importance in setting up the new provisions.

Consideration should be given to introducing requirements for monitoring and documentation of concentrations in outgoing wastewater of all active substances produced at a facility. This would also entail that a validated method for measuring active substances would need to be established. The process for the coming prioritization of new substances for regulation could be, as a first step, to introduce a general limit for the emission of active substances in manufacturing corresponding to what applies to applications for authorization of medicinal products. This would eliminate any necessity to gather environmental data for individual substances. In a later phase, when environmental data might be required or become available in some other manner, substance-specific limits can be established for priority substances.

To facilitate work to identify candidates for maximum emission levels, information is needed about environmental impact. One way to collect environmental information about pharmaceutical substances could be to introduce a database, which was also arrived at in the Medical Product Agency’s 2004 governmental commission. This should be maintained by the EU medicinal products authority, the European Medicines Agency, EMA, in a manner corresponding to the database in Reach that is run by ECHA (the European Chemicals Authority).

Other processes in Reach can also be borne in mind when structuring the new medicinal products regulations. One example would be to set up a candidate list. Such a public list can function as a kind of Nota Bene list of substances placed under special observation. It is also important for both the EU authority and individual Member Countries to be permitted to set up a certain substance in the legislation. Here, too, Reach can provide inspiration.
# 6 Abbreviations, definitions, and explanations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
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<tr>
<td>BAT</td>
<td>Best Available Technique</td>
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<tr>
<td>COD</td>
<td>Chemical Oxygen Demand (a measure of the amount of oxygen consumed in complete chemical degradation of organic substances in wastewater)</td>
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<tr>
<td>COMMPS</td>
<td>Combined Monitoring-based and Modelling-based Priority Setting</td>
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<tr>
<td>ECHA</td>
<td>European Chemicals Agency</td>
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<tr>
<td>EDQM</td>
<td>The European Directorate for the Quality of Medicines and Health Care</td>
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<tr>
<td>EFPIA</td>
<td>European Federation of Pharmaceutical Industries and Associations</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<td>EPAR</td>
<td>European Public Assessment Report</td>
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<tr>
<td>ERC</td>
<td>Environmental Reference Concentration</td>
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<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>FGL</td>
<td>The Association for Generic Pharmaceuticals in Sweden (Föreningen för generiska läkemedel)</td>
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<tr>
<td>UN</td>
<td>United Nations</td>
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<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<td>IED</td>
<td>Industrial Emissions (Integrated Pollution Prevention and Control)</td>
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<td>IMPEL</td>
<td>The European Union Network for the Implementation and Enforcement of Environmental Law</td>
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<tr>
<td>IPPC</td>
<td>Integrated Preventive Pollution Control</td>
</tr>
<tr>
<td>KD</td>
<td>Kronans droghandel? (private pharmacy company)</td>
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<tr>
<td>COM</td>
<td>European Commission</td>
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<tr>
<td>LIF</td>
<td>Research-based Pharmaceutical Companies in Sweden (Läkemedelsindustriföreningen)</td>
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<td>MIS</td>
<td>Miljömärkning i Sverige? (Miljökonsekvensbeskrivning)</td>
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<tr>
<td>MKB</td>
<td>Environmental Consequence Statement</td>
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<td>NGO</td>
<td>Non Governmental Organization</td>
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<td>OFC</td>
<td>Organic Fine Chemicals</td>
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<td>PEC</td>
<td>Predicted Effect Concentration</td>
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<tr>
<td>PETL</td>
<td>Patancheru Enviro Tech Limited (A water purification plant in India)</td>
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<td>PIC/S</td>
<td>Pharmaceutical Inspection Co-operation Scheme</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
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<tr>
<td>PhRMA</td>
<td>The Pharmaceutical Research and Manufacturers of America</td>
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<td>PNEC</td>
<td>Predicted No Effect Concentration</td>
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<tr>
<td>POPs</td>
<td>Persistent Organic Pollutants (under the Stockholm Convention)</td>
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<td>PSCI</td>
<td>Pharmaceutical Supply Chain Initiative</td>
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<td>RPS</td>
<td>Relevans, Potential, Styrbarhet (Relevance, Potential, Controllability)</td>
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<tr>
<td>SLL</td>
<td>Stockholm County Council (Stockholms läns landsting)</td>
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<td>SVHC</td>
<td>Substance of Very High Concern (concept under Reach)</td>
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<tr>
<td>TFEU</td>
<td>Treaty on the Functioning of the European Union</td>
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<td>TOC</td>
<td>Total Organic Carbon (a measure of the total organic carbon content in water)</td>
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<tr>
<td>TVL</td>
<td>Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket)</td>
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<tr>
<td>VGR</td>
<td>Western Götaland Region (Västra Götalandsregionen)</td>
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