Assessing and quantifying the pharmaceutical supply chain and its environmental impacts

Master thesis - Gidde Tuitert
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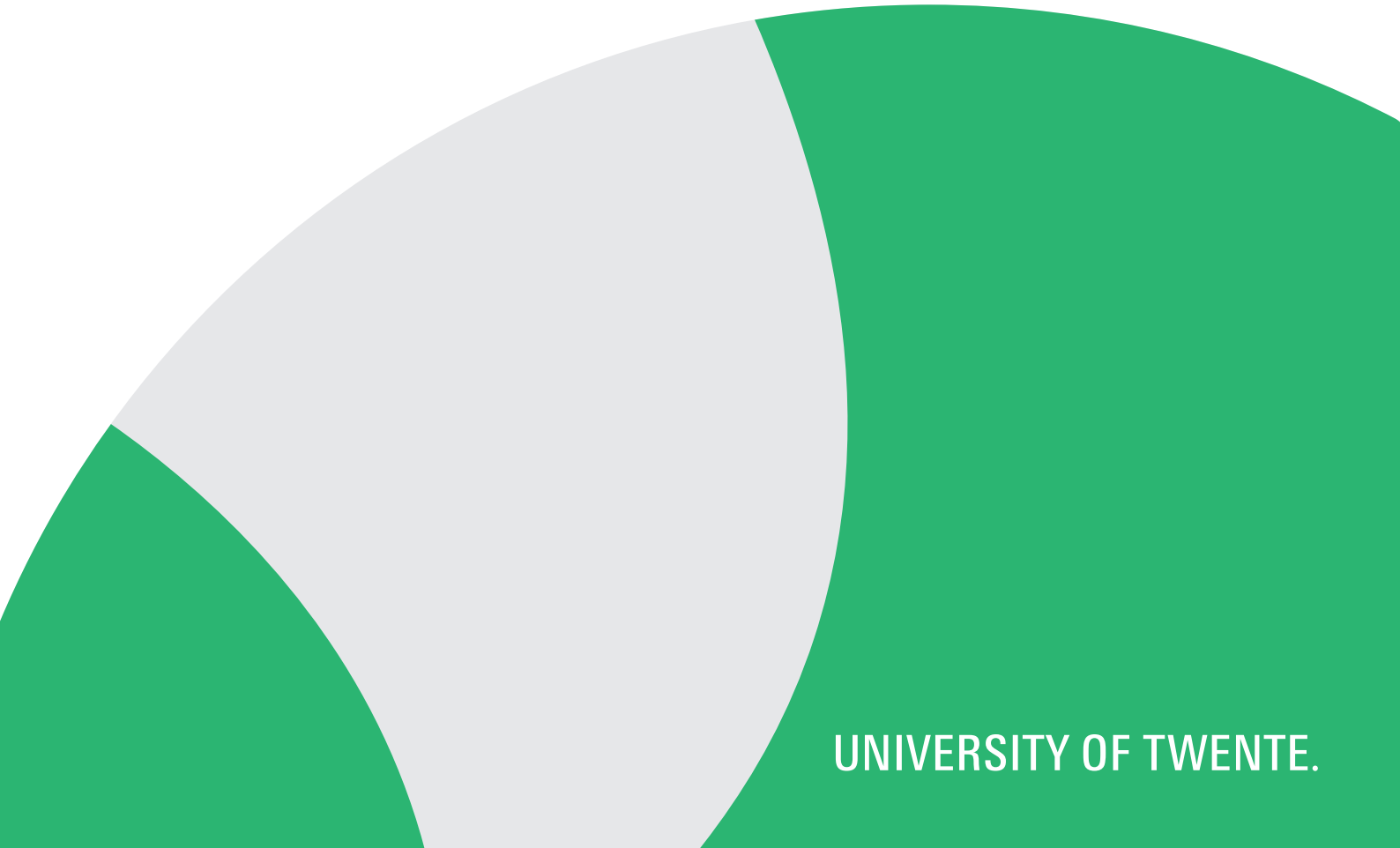

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Assessing and quantifying the pharmaceutical supply chain and its environmental impacts

MSC. CIVIL ENGINEERING AND MANAGEMENT

WATER ENGINEERING AND MANAGEMENT

MASTER THESIS

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Preface

This study represents the final stage of my MSc Civil Engineering and Management at the University of Twente. In this research, I assessed and quantified the environmental impact of pharmaceutical manufacturing. This project was done at the Water Engineering and Management research group at the University of Twente, under the supervision of Lara Wöhler MSc. and Dr. Maarten Krol.

I am extremely grateful to my supervisors Lara Wöhler MSc. and Dr. Maarten Krol, who have been instrumental in the completion of this research. I would like to thank Lara Wöhler MSc. for all her helpful input and continuous guidance throughout the process. Many thanks to Dr. Maarten Krol for his insights in how to approach this research, given its many iterations, and the valuable meetings.

I would like to express my gratitude to those who contributed to this research. Special thanks to Dr. Narasimha Reddy Donthi and Stan Cox for their help in understanding the situation in Patancheru, India and the provision of valuable information. Many thanks to Brittany Doody from Rx-360 for her help and efforts in getting input from a great number of pharmaceutical organisations. I would also like to thank Guy Villax, CEO of Hovione, for his insights into the pharmaceutical industry and for sharing his experiences on the topic. And many thanks to SFK, who provided pharmaceutical market share information for the Netherlands. I would like to express my gratitude to all those who went out of their way to provide input for this research, in spite of the (seemingly) sensitive nature of this topic.

I would also like to recognise those with whom I had valuable discussions as well as relaxing moments during (online) coffee breaks. A special thanks to Jurgen and Thomas for the valuable input over the course of this research project.

Finally, I am incredibly grateful to my friends and family for their continuous support during my studies and master thesis. This especially holds for my family, who supported me through all my endeavours and without whom this would not have been possible.

Gidde Tuitert
Enschede - 8th January, 2021

Abstract

Pharmaceuticals in the environment is a topic that gets increasingly more attention. Impacts are not only local, but also on a global level through e.g. the promotion of antimicrobial resistance. In this context, urban wastewater is often seen as one of the most important pathways for pharmaceuticals to enter the environment. Nevertheless, it has been shown that manufacturing effluents can contain considerable amounts of pharmaceutical residues. Impacts of these kinds of local pollution can be severe, but the full extent of the problem is unknown. In this research, the production-related environmental impact of European pharmaceutical consumption is assessed. This is done for the active pharmaceutical ingredients (APIs) ciprofloxacin and metoprolol.

In the first stage, public access to the pharmaceutical supply chain is assessed by contacting relevant organisations and authorities. The second stage is comprised of estimating supply chains through the analysis of trade data. Lastly, the environmental impact of pharmaceutical manufacturing is examined for two substantiated example pharmaceuticals (ciprofloxacin and metoprolol) in a specific manufacturing hotspot in Patancheru, India. A grey water footprint (GWF), which describes the amount of water needed to assimilate pollutants, is consequently calculated for European consumption.

Results demonstrate that the pharmaceutical supply chain is nontransparent to the public and researchers, even when confidentiality regarding the source is assured. Data on the supply chain is deemed confidential and pharmaceutical organisations and regulatory agencies are not willing or allowed to share information. An analysis of the supply chain using trade data shows that Germany is a considerable exporter of finished pharmaceutical products (FPPs) related to ciprofloxacin and metoprolol (a share of almost 15%). China is a substantial exporter of the studied APIs, with a share of around 30%. Quantification of production-related environmental pollution indicates that the average European consumer is responsible for a GWF of 18.8 m^3/year for ciprofloxacin and 0.0055 m^3/year for metoprolol. This is relatively minor when compared to the total Dutch and German GWF of the respective pharmaceuticals (a share of 0-3%). Yet, local environmental impacts are potentially substantial since loads are concentrated at production locations. Consequently, indirect impacts are on a global level, with the promotion of antimicrobial resistance as the most notable example.

This study highlights the complexity and sensitive nature of the pharmaceutical supply chain. In addition, it quantifies environmental pollution caused by this industry. The need for concrete measures is highlighted, which include an increase in transparency of the supply chain, the incorporation of environmental criteria in the regulatory framework and the stimulation of self-regulation.

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Acronyms

Amberpet STP	Amberpet sewage treatment plant
AMR	antimicrobial resistance
API	active pharmaceutical ingredient
DDD	Defined Daily Dose
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FPP	finished pharmaceutical product
GMP	Good Manufacturing Practices
GWF	grey water footprint
HS	Harmonized Commodity Description and Coding System
NCA	national competent authority
PETL WWTP	Patancheru Enviro Tech Ltd. wastewater treatment plant
PNEC	Predicted No-Effect Concentration
SFK	Stichting Farmaceutische Kengetallen
TDS	total dissolved solids
UN	United Nations
US	United States
WHO	World Health Organization
WPL	water pollution level

1. Introduction

1.1 Background

Pharmaceuticals' benefit to society cannot be disputed: In Europe over the last century, they have contributed to an increase in life expectancy by 30 years and a reduction in the mortality rate of diseases including HIV/AIDS and a number of cancers (EFPIA, 2019). In spite of this, their extreme bioactivity does not only make them beneficial to society, but also potentially harmful. This is especially dangerous if pharmaceuticals are found in the environment, which has been the case in all five United Nations (UN) groups, covering 71 countries (aus der Beek et al., 2016). Detected in ground-, surface- and drinking water, pharmaceuticals or mixtures thereof have the potential of posing significant risk to ecosystems and human health (aus der Beek et al., 2016; BIO Intelligence Service, 2013; Ezechiáš et al., 2016; Marsland & Roy, 2016; Sanderson et al., 2004). Different pharmaceutical classes have different effects due to their individual bio-chemical properties. For example, sex hormones have the potential of causing a multitude of unwanted effects on aquatic life. These include the changing of fishes' reproductive abilities to feminisation of male populations to an increased mortality rate at extreme concentrations (Sanderson et al., 2004; Santos et al., 2010; Xu et al., 2008). As a result, a selection of sex hormones has now been added to the European Union's pollutant watch list (Guo et al., 2016). Human exposure to certain pharmaceuticals, such as some chiral pharmaceuticals[1] and (abnormally) high levels of estrogens, has been associated with the occurrence of certain types of cancer (Liang & Shang, 2013; Zhou et al., 2018). Despite this, human exposure to (individual) pharmaceuticals in the environment is generally thought to cause no significant health concerns (European Commission, 2015; World Health Organization, 2017). This does not imply that human health problems due to pharmaceuticals in the environment cannot occur, either now or in the future. This is especially true for long-term effects and mixtures of pharmaceuticals, as the exact ecological and human impacts of these so-called cocktails are not well understood (BIO Intelligence Service, 2013; Cleuvers, 2003; Deloitte, 2018; European Commission, 2015; Greenpeace, 2004; Morley, 2009; Quinn et al., 2009; Sanchez et al., 2011; Yin et al., 2017).

Besides their potential ecotoxicity, antibiotics in the environment constitute an increased concern due to the rise of antimicrobial resistance (Crane et al., 2006; Janecko et al., 2016; Kümmerer, 2009; Rodrigues et al., 2019). In a report commissioned by the British government in 2014, it was estimated that antimicrobial resistance (AMR) might become the leading cause of death worldwide by 2050 (Gaze, 2017; Neill, 2014). Moreover, the United Nations report that "uncontrolled antimicrobial resistance could be comparable to the shocks experienced during the 2008-2009 global financial crisis" (IACG, 2019). Although antibiotic concentrations found in nature are significantly lower than in raw effluent from e.g. hospitals, it has been found that even in low concentrations AMR is able to develop (Gullberg et al., 2011; Kümmerer, 2009). This makes it not only a problem for areas where

[1] When a substance is chiral, its mirror image cannot be superimposed over itself (Zhou et al., 2018). As described by Sanganyado et al. (2017), each enantiomer can have different effects on the body, as well as have different toxicity. Around 50% of pharmaceuticals in use are chiral (Sanganyado et al., 2017).

concentrations are high, but also there were concentrations are much lower.

Globally, the origin of pharmaceuticals in the environment has been mainly attributed to urban wastewater (aus der Beek et al., 2016). Consequently, urban wastewater as a pathway for pharmaceutical pollution has been researched extensively (Brezina et al., 2017; Corominas et al., 2020; Mohapatra et al., 2016; Pouzol et al., 2020). This impact has also been quantified using the grey water footprint (GWF) (Martínez-Alcalá et al., 2018; Wöhler, Niebaum, et al., 2020). A tool coined by Hoekstra et al. (2011), the GWF shows the amount of water that is needed to assimilate pollutants that enter the water body, given existing natural background concentrations and water quality standards. It is part of the overarching water footprint concept, which is a tool for the accounting of all water that is used in a product's production process and supply chain. Since it includes both a spatial and temporal dimension, it can be mapped on a geographic and temporal level (Hoekstra et al., 2011).

As of yet, assessment and quantification of pharmaceutical pollution has been mainly performed for urban wastewater. In spite of this, aus der Beek et al. (2016) notes that other sources, such as manufacturers, hospitals or agricultural areas, can play a significant role on a local level. To combat the emission of pharmaceuticals into the environment, the European Union (EU) has started taking steps to reduce pharmaceutical emissions during the whole pharmaceutical life cycle (European Commission, 2019b, 2020b; More, 2020). Whereas these measures are mostly constrained to industries or applications within EU borders, like most sectors, the pharmaceutical industry has gone global: Pharmaceuticals for the European consumer are produced all over the world. As a result, the impact and consequently responsibility of the European consumer is not limited to the EU's borders. In manufacturing hotspots across the world, including those that export to the EU, pharmaceutical concentrations above environmental quality standards have been measured (Bielen et al., 2017; Fick et al., 2009; Larsson et al., 2007; Sim et al., 2011). High pharmaceutical concentrations in manufacturing effluents can pose potential harm to the environment. This is evident in the case of Sanchez et al. (2011), who found signs of endocrine disruption in fish living downstream of pharmaceutical manufacturing discharges. Negative effects of environmental contamination have also been reported by organisations such as Greenpeace, Changing Markets and Ecostorm. As described by Greenpeace (2004), people living in the heavily industrialised Medak district in India are more likely to become ill than control groups. In the region, which also accommodates pharmaceutical manufacturers, "morbidity figures due to pollution related illnesses like cancer, asthma and bronchitis and heart diseases" were found to be higher than in other regions (Greenpeace, 2004). Likewise, Changing Markets & Ecostorm (2016) have criticised the pharmaceutical industry for its role in contaminating the environment and the subsequent impact on communities in India. Apart from local impacts, the emission of antibiotics path the way to global antimicrobial resistance: manufacturing effluents or receiving water bodies have been found to contain considerable amounts of multidrug resistant bacteria (Li et al., 2009; Lübbert et al., 2017; Thai et al., 2018).

Although located outside of its jurisdiction, the EU has the power to enforce environmental stewardship from its pharmaceutical manufacturers: To manufacture pharmaceuticals for the European market, Good Manufacturing Practices (GMP) have to be followed. This holds for both of the two major pharmaceutical production stages: manufacturing of the active pharmaceutical ingredient (API) and of the finished pharmaceutical product (FPP). Multiple GMPs exist, including those from the EU, the United States (US) and the World Health Organization (WHO). Although GMPs do focus on the manufacturing and quality of pharmaceuticals, they barely take into account the risks that these products may impose on the environment at the manufacturing stage (although the WHO gives increasingly more attention to the prevention of AMR) (European Environmental Bureau, 2018; FDA, 2018; U.S. Department of Health and Human Services, 2017; World Health Organization, 2019). As mentioned by Larsson (2014), Sweden proposed to add environmental criteria to the European GMP. While Environmental Risk Assessments are mandatory for a pharmaceutical's market entry, they are not included in the actual decision making process (European Environmental Bureau, 2018;

Walter & Mitkidis, 2018). In addition, Environmental Risk Assessments of human pharmaceuticals are only mandatory for those products that entered the market after 2005 and environmental risk mitigation measures are not compulsory (European Environmental Bureau, 2018). It is concluded that in the current situation, the responsibility for environmental stewardship mainly lies with the manufacturer and its host country's legislation.

1.2 Research objectives

It has been illustrated that the environmental impact of pharmaceuticals in manufacturing effluent is potentially severe, but does not get widespread attention. A lack of transparency in the pharmaceutical supply chain exacerbates this, as it prohibits European consumers from making informed decisions (Larsson & Fick, 2009). A thorough search of relevant literature has revealed no systematic study into the supply chains of pharmaceuticals for the European market. Consequently, the environmental burden of this supply chain has not been quantified. This makes it difficult to understand the severity of the problem and although the effects from this kind of pollution are not immediately visible to the (European) consumer, all are affected by it in the long term.

The objective of this study is to investigate and describe the supply chains of pharmaceuticals on the European[2] market. The impact of these supply chains on the environment is subsequently quantified with the GWF as its indicator.

The following research question has been defined: What is the average European consumer's environmental impact resulting from pharmaceutical manufacturing?

This question is answered with the following subquestions:

1. What information regarding the pharmaceutical supply chain and its environmental impact is (publicly) accessible?
2. How is the pharmaceutical supply chain for the European market organised and where are manufacturers located?
3. What is the production-related GWF of human pharmaceuticals for the European market and how does this relate to the European consumer?

[2] In this study, 'European' refers to countries that are member states of the European Union (EU) and that are bound to its rights and obligations.

2. Methodology

In this section, the study's methodology is described. Figure 1 illustrates a basic outline of the steps that are taken to answer the subquestions and consequently, the research question.

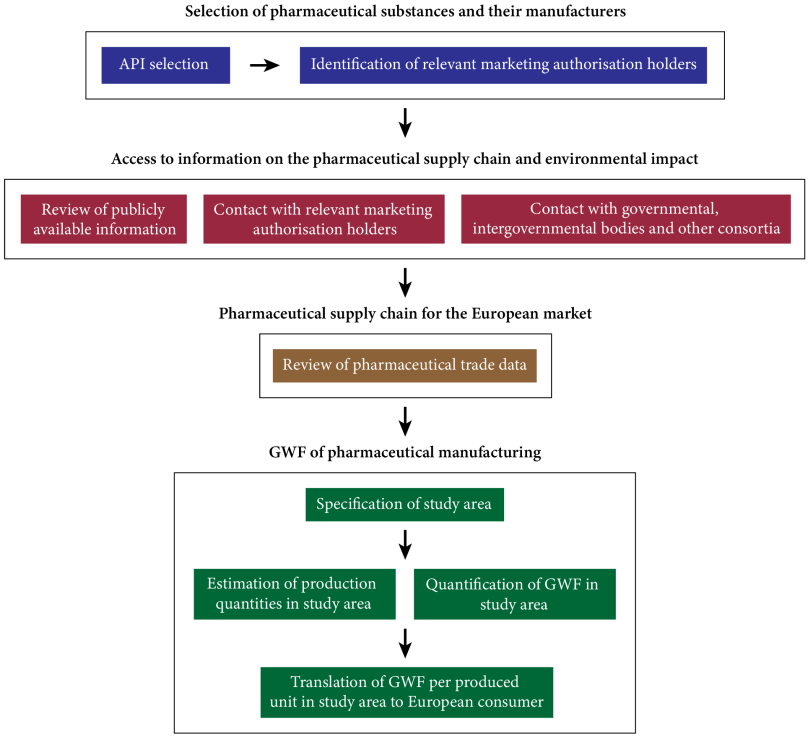

Figure 1: Research steps taken to quantify the European production-related GWF

To accurately interpret the scope of this research, an overview of the pharmaceutical manufacturing supply chain stages is given in Figure 2. The supply chain can generally be divided into two stages: primary and secondary manufacturing. These stages correspond to the API and FPP production stages, respectively (Shah, 2004). The primary production stage involves the use or formulation of API starting materials. As defined by the ICH (2000), an API starting material is a "raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API". In this study, focus was put on pharmaceutical pollution due to the release of APIs into the environment. Therefore, only API and FPP production was considered, which do not include primary production stages such as formulation of raw materials or intermediates.

Another important consideration is that the marketing authorisation holders[1] mentioned in the first

[1] As defined by the European Medicines Agency (n.d.-c): "The company or other legal entity that has the authorisation to

step of Figure 1 are the companies that bring the FPPs to market. It is possible, however, that other manufacturers (e.g. contract manufacturers) are active in the supply chain. In this study, the term 'manufacturers' signifies those companies that take part in the pharmaceutical manufacturing supply chain but are not necessarily the companies that have obtained approval to market the FPP.

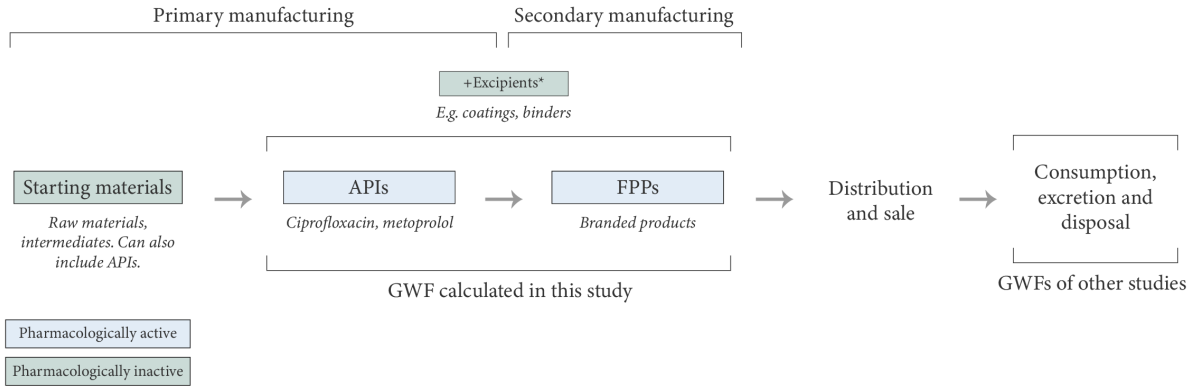

Figure 2: An outline of the pharmaceutical manufacturing supply chain, partly based on Haywood & Glass (2011); ICH (2000); Shah (2004); World Health Organization (2014). *Although excipients are generally classified as inactive ingredients, they can substantially affect a pharmaceutical's pharmacodynamic and pharmacokinetic properties (Bhattacharyya et al., 2006; Gerber et al., 2018; Haywood & Glass, 2011).

2.1 Selection of pharmaceutical substances and their marketing authorisation holders

The first step in understanding the environmental impact of pharmaceutical manufacturing was to get an overview of the available data. This manufacturing supply chain is different for each pharmaceutical API and FPP. Since it was not feasible to consider all APIs, which are a few thousand (G. Villax, personal communication, November 25, 2020), those deemed most relevant were selected for this research. The following criteria were used for this selection:

- Availability of concentration data in manufacturing effluents: based on studies covering this topic.
- Consumption of the pharmaceuticals in the EU: described with European pharmaceutical consumption data.
- Importance to society: assessed using the WHO Model List of Essential Medicines and the WHO list of critically important antimicrobials.
- Environmental impact: assessed using the European surface water Watch List under the Water Framework Directive.
- Complexity of the production process: based on the perceived complexity of the production process and the number of available dosage forms[2].

market a medicine in one, several or all European Union Member States.".

[2]Less complexity in the production process and fewer dosage forms are preferred, since they are likely to correspond with less complex supply chains.

For the selected APIs (ciprofloxacin and metoprolol), relevant marketing authorisation holders of products containing the APIs were identified. Relevance of marketing authorisation holders is based on their API-specific market share. The preferred approach to acquire information on pharmaceutical supply chains and environmental impact was to perform a global and/or regional market analysis using market analysis reports. Since this did not yield adequate results, contact was sought with European statistical organisations: Pharmaceutical consumption is measured in the majority (if not all) European countries and some of the relevant organisations also hold data on the used brands (and consequently, the related marketing authorisation holders).

2.2 Access to information on the pharmaceutical supply chain and environmental impact

Access to information on the pharmaceutical supply chain was assessed by reviewing publicly available information and contacting organisations that could potentially provide information on the supply chain and its impacts. First, public information was assessed by reviewing (scientific) literature, newspaper articles and public databases on pharmaceutical products (e.g. national registers of authorised medicines). Second, the previously identified marketing authorisation holders were asked to provide the following information concerning the production of their ciprofloxacin and/or metoprolol products: 1) the production steps, locations and partners involved, 2) the processes where surface water pollution could occur and 3) the quality and quantity of effluents. Third, since the pharmaceutical sector is a complex and tightly regulated industry, with legislation covering almost every aspect of a pharmaceutical's life cycle, governmental organisations, intergovernmental organisations and other types of consortia were also contacted.

In the EU, a pharmaceutical product can be approved for market entry through a number of approaches: the centralised, decentralised, mutual-recognition or national procedure. In the centralised procedure, the applicant submits a proposal to the European Medicines Agency (EMA). Following this, the EMA conducts the marketing approval process, after which it gives a recommendation to the European Commission. Subsequently, the European Commission gives an approval or disapproval to the applicant for the marketing of the pharmaceutical product in all EU member states and Iceland, Liechtenstein and Norway (European Medicines Agency, n.d.-a). In the decentralised and mutual recognition procedure, marketing approval is sought for a number of European member states at the same time (European Commission, 2007). In the national procedure, the applicant submits a proposal to a single country. In this case, the country's own regulatory body (national competent authority (NCA)) performs the approval process and decides on the product's marketing authorisation for their respective nation only (European Medicines Agency, n.d.-a).

Part of the European marketing approval process is compliance with the European GMP. The European GMP are a set of codes, guidelines and principles that depict the minimum requirements that manufacturers should adhere to. Laid out in Directive 2003/94/EC, they do not consider the environmental impact of manufacturers. However, they do require the manufacturer to maintain a documentation system. This is detailed more clearly in Volume 4 of the Good Manufacturing Guidelines, where an interpretation of the GMP is given. According to the European Commission (2014b), records should be kept of "The name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates or labeling and packaging materials for API's; the name of the supplier...". Furthermore, the European Commission (2014a) states that "The supply chain and traceability records for each active substance (including active substance starting materials) should be available and be retained by the EEA based manufacturer or importer of the medicinal product.". In Directive 2003/94/EC, it is furthermore stated that "Data stored by those systems shall be made

readily available in legible form and shall be provided to the competent authorities at their request.", where “those systems” refers to “electronic, photographic or other data processing systems”. In short, this means that marketing authorisation holders are obliged to document their supply chain, and provide this information to authorities at their request. Since marketing authorisation might have taken different routes for the market entry of their specific ciprofloxacin and/or metoprolol product(s), a request for supply chain information was made with both intergovernmental bodies and NCAs.

2.3 Pharmaceutical supply chain for the European market

As mentioned in the previous section, the preferred way of mapping the pharmaceutical supply chain was using information from pharmaceutical marketing authorisation holders and/or governmental and intergovernmental bodies. Another approach, more alike to a top down approach, is using trade data to visualise pharmaceutical trade flows. Trade data of close to 200 countries, based on the 6-digit Harmonized Commodity Description and Coding System (HS), are collected by the United Nations (United Nations, n.d.; United Nations Department of Economic and Social Affairs, 2019). Incorporated in the Comtrade database, this data provides valuable information on the trade of commodities. However, as mentioned by the United Nations (n.d.), imports and exports generally do not match as they are measured differently. Gaulier & Zignago (2008) state that the reliability of country reports and the fact that oftentimes two figures for the same flow are reported (i.e. import and export between the same countries) can be used to improve the accuracy of the data. For this reason, the BACI data provided by CEPII was used. This dataset is based on the Comtrade data, but has undergone several processing steps to come to more representative values for the trade between countries (Gaulier & Zignago, 2008).

Although the 6-digit HS provides relatively descriptive commodity categories, it does not specify individual APIs. Furthermore, APIs have been found to fit in a variety of different HS categories. To gain better insights into the categories that pharmaceutical substances belong to, a number of organisations such as the European Trade Agency, the Dutch Chamber of Commerce and the Dutch customs agency were contacted. Using their input and publicly available information, the following categorisation was found (descriptions are based on EU regulation (European Commission, 2019a)):

- The API ciprofloxacin or ciprofloxacin HCL[3]
  - HS 293359 (European Commission, 2019a)
    A subset of the heterocyclic compounds group.
  - HS 294190(30) (Ministry of Commerce & Industry, 2020)
    The antibiotic subset of the 'other organic compounds' group. The 8-digit HS code (HS 29419030: Ciprofloxacin and its salts) is likely to be specific for trade with India.
- FPPs containing ciprofloxacin or ciprofloxacin HCL
  - HS 300420 (Tax and Customs Administration of the Netherlands, personal communication, September 30, 2020)
    The antibiotic subset of medicaments in measured doses or for retail sale.
  - HS 30042013 (DGCI&S, n.d.)
    The Indian trade statistics portal mentions this as an 8-digit HS code for “Ciprofloxacine - In capsul, tblts form etc”. This is likely to be a specific code for trade with India.

[3]Ciprofloxacin HCL is a salt formation of ciprofloxacin and contains the same API. Salt formations can have a variety of advantages over the ‘regular’ version (Verbeeck et al., 2006).

  - HS 30042033 (DGCI&S, n.d.)
    The Indian trade statistics portal mentions this as an 8-digit HS code for "Ciprofloxacin (Fluoroquinolones)". This is likely to be a specific code for trade with India. The code has been used in customs declarations (Port Examiner, 2013a).
  - HS 300320 (Tax and Customs Administration of the Netherlands, personal communication, September 30, 2020)
    The antibiotic subset of medicaments not put in measured doses or for retail sale.
  - HS 300490 (Port Examiner, 2013b)
    The 'other' subset of medicaments in measured doses or for retail sale.
  - HS 300390 (assumption based on previous HS codes)
    The 'other' subset of medicaments not put in measured doses or for retail sale.

- The API metoprolol
  - HS 292219 (European Commission, 2019a)
    A subset of the oxygen-function amino-compounds group.

- FPPs containing metoprolol (incl. metoprolol succinate and metoprolol tartrate)[4]
  - HS 300490 (European Commission, 2020a; Port Examiner, 2014b, 2015)
    The 'other' subset of medicaments in measured doses or for retail sale.
  - HS 30049074 (DGCI&S, n.d.)
    The Indian trade statistics portal mentions this as an 8-digit HS code for "Propranolol, Metoprolol, Atenolol and Labetalol". This is likely to be a specific code for trade with India. The code has been used in customs declarations (Port Examiner, 2014a).
  - HS 300390 (assumption based on previous HS codes)
    The 'other' subset of medicaments not put in measured doses or for retail sale.

The 6-digit HS codes are aggregates of a variety of chemicals and/or pharmaceuticals. For example, HS code 300420 specifies commodities that are: *"Medicaments (excluding goods of heading 3002, 3005 or 3006) consisting of mixed or unmixed products for therapeutic or prophylactic uses, put up in measured doses (including those in the form of transdermal administration systems) or in forms or packings for retail sale: Other, containing antibiotics"*. In the case of HS code 300420, an estimation of the ratio of ciprofloxacin could be made using antibiotic consumption data of a variety of countries (refer to Appendix A). This led to a share of 1 to 10% (based on ciprofloxacin and antibiotic consumption patterns and with mass and Defined Daily Dose (DDD) as indicators).

This estimate provides a rough indication of ciprofloxacin's share in HS 300420. Unfortunately, this same approach could not be taken for other HS categories, as information on the specific commodities in these categories is even scarcer than in HS code 300420. For this reason, no estimates were made for ciprofloxacin's and metoprolol's share in their overarching categories, and following this, no conclusions are drawn specifically for these FPPs or APIs.

A number of points should be addressed for an accurate interpretation of the trade data. First, some HS code categories are more commonly used than others. Although this can be partly attributed to the fact that some pharmaceuticals are traded more intensively, it is also caused by the scope of HS codes. For example, as shown in Figure 3, HS 300490 is an outlier in terms of quantity. This is likely explained by the fact that this is an ambiguous category, where pharmaceuticals are categorised under if they do not seem to fit other categories. Second, the 8-digit HS codes mentioned at the beginning of

[4] Metoprolol succinate and metoprolol tartrate are different salt forms of metoprolol.

this section are based on Indian trade data and are therefore, most likely, only applicable to trade with India. As a result, they are only used to comment on trade flows associated with India.

To illustrate which countries are most involved with either export or import of the studied products, each nations' balance of trade[5] was also calculated. This was done by summing the countries' export and import of relevant HS codes and subtracting total imports from total exports.

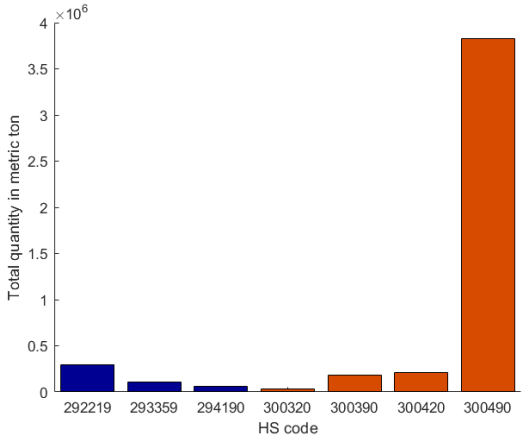

Figure 3: Total trade quantity in tons of the selected HS codes (HS codes associated with APIs in blue and those associated with FPPs in red)

2.4 The GWF of pharmaceutical manufacturing

The pharmaceutical industry's production-related environmental impact was quantified using the GWF. A specific study area was examined, which was specified on the basis of scientific literature and the presence of information concerning manufacturers operating in the area. In the first step, the study area's production quantity with regards to ciprofloxacin and metoprolol was estimated. Second, the GWF was calculated for both substances and related to their respective production quantities. Third, the GWF for the pharmaceutical's entire production quantity was translated to the GWF per ciprofloxacin and metoprolol DDD. Fourth, the GWF per DDD was related to the European consumer using Dutch, German, Finnish and Norwegian consumption data. For this, it has been assumed that the GWF of ciprofloxacin and metoprolol production in the study area is representative for ciprofloxacin and metoprolol production in general.

To specify the study area and acquire input for the GWF calculation, a variety of reports were considered (e.g. Larsson et al. (2007), Fick et al. (2009), Sim et al. (2010), Ashfaq et al. (2017) and Thai et al. (2018)). It was found that for the studies of Larsson et al. (2007), Fick et al. (2009), Gothwal & Shashidhar (2016) and Lübbert et al. (2017) sufficient data was available concerning pharmaceutical concentrations and manufacturing in their respective region (Patancheru, Hyderabad, India). India has made a considerable amount of environmental and pharmaceutical licensing data public, which makes identification of manufacturers easier. Furthermore, the country is considered one of the most important players in the pharmaceutical industry (Balakrishna et al., 2017; Cox, 2007; Larsson, 2008). The Patancheru region in particular hosts a number of large pharmaceutical manufacturers and it is reported that a large portion of India's bulk drug industry takes place here (some estimates reaching 35 to 40% (Cox, 2007)) (Changing Markets & Ecostorm, 2016; Cox, 2007; Siddiqui, 2016; Tremblay, 2011). This does seem to come at a cost, however, as the region has received

[5]Whereas the balance of trade is normally defined in monetary terms, quantities (in tons) are used in this study.

widespread attention from the scientific community, the (international) press and other organisations for the extent of environmental pollution (Larsson et al., 2007; Lübbert et al., 2017; Mohan, 2020; Nordea & Changing Markets, 2018; Siddiqui, 2016; Swedwatch, 2020). Considering these points, it was decided to quantify the GWF of ciprofloxacin and metoprolol using the situation in Patancheru, India. More specifically, the GWF is based on those manufacturers that supplied wastewater at the time of sampling to (one of) the sampling sites: Patancheru Enviro Tech Ltd. wastewater treatment plant (PETL WWTP).

2.4.1 Estimating production quantities

Two different approaches were followed for the estimation of production quantities in the Patancheru area: the bottom-up and top-down approach. To obtain a final production quantity, results from the bottom-up and top-down approach were subsequently arithmetically averaged. In the bottom-up approach, manufacturers in the region were identified. Their links to the sampling sites were examined, as well as production quantities and export licenses for the EU. For this quantitative and qualitative data collection and analysis, input was gathered through the following pathways:

- Contact with the respective studies' authors.
- Contact with manufacturers, governmental organisations, trade organisations and other types of supraorganisations.
- Examination of publicly accessible information, such as trade databases, studies or journal articles and news reports.

In the top-down approach, production of the studied pharmaceutical APIs and FPPs in the study area was estimated using trade data. For this, the assumption was made that national consumption of the produced pharmaceuticals was negligible and that all produced pharmaceuticals were exported. BACI data from CEPII provides quantities and monetary values of India's export with regards to the 6-digit HS codes specified in the previous section. DGCI&S (n.d.) describes monetary values of more specific 8-digit HS categories for ciprofloxacin and metoprolol (refer to the overview in the previous section). Combining both data sources led to Indian export quantities of specific ciprofloxacin and metoprolol products. To that end, it was assumed that all 8-code pharmaceuticals in a 6-digit HS code category have the same monetary value per unit of weight: e.g. HS 30042033 and HS 30042080 have the same monetary value per unit of weight as HS 300420. Furthermore, data in the Indian trade portal was only available from 2014 on and not for 2006 or 2008, which are the years sampling took place. For this reason, the same year (2018-2019) as that of the considered BACI dataset was used. Given the relative stability of Indian export of the overarching HS codes (refer to Appendix D.1), this was considered a plausible assumption. Total Indian production quantities were subsequently translated to production in the Patancheru region using a rough estimate by Cox (2007). Cox (2007), who wrote extensively on the topic and the situation in Patancheru in particular, estimated that 35-40% of India's bulk drug are manufactured in Patancheru.

2.4.2 Quantification of the GWF

For the calculation of the final GWF, Equation 2.1 was used (Hoekstra et al., 2011).

$$GWF = \frac{c_{effl} - c_{act}}{c_{max} - c_{nat}} * Q_{effl} \tag{2.1}$$

where c_{effl} [µg/L] is the concentration of the pharmaceutical in the effluent. c_{act} [µg/L] is the concentration of the pharmaceutical in the intake water and in this case, equal to zero. c_{max} [µg/L] is the maximum acceptable concentration in the receiving water body. c_{nat} [µg/L] is the natural background concentration in the receiving water body, which is zero for human-made pharmaceuticals (Hoekstra et al., 2011). Lastly, Q_{effl} [m^3/year] is the discharge of effluents from PETL WWTP into the receiving water body. For this, it was assumed that the influent discharge at PETL WWTP equals its effluent discharge (there is no loss of water in the treatment process).

Ciprofloxacin
For c_{effl}, PETL WWTP effluents showed concentrations of 14 000 µg/L in the study of Fick et al. (2009) and 28 000 to 31 000 µg/L in the study of Larsson et al. (2007). For this research, this was averaged to a value of 21 750 µg/L. The situation in 2015 was assessed using a study by Gothwal & Shashidhar (2016), where ciprofloxacin was measured at the inlet and outlet of the Amberpet sewage treatment plant (Amberpet STP)[6]. This led to a concentration of 5015.6 and 275.07 µg/L, respectively[7]. For c_{max}, the AMR Industry Alliance (2018) mentions 0.064 µg/L as the limit for protection against antimicrobial resistance, which is based on the study by Bengtsson-Palme & Larsson (2016). Regarding ecotoxicity, the AMR Industry Alliance (2018) states a Predicted No-Effect Concentration (PNEC) of 0.45 µg/L. Sahlin et al. (2018) suggest 0.1 µg/L as sufficiently protective for both the environment and protection against antimicrobial resistance development. Given the diverging thresholds regarding environmental quality standards, the most conservative maximum concentration was adopted in this study. This corresponds to 0.064 µg/L. Q_{effl} was approximated by averaging the total 2007 and 2008 influent at PETL WWTP, which resulted in 589275 m^3/year (Central Pollution Control Board, n.d.). This is similar to the daily PETL WWTP effluent discharge of 1500 m^3/day mentioned by Larsson et al. (2007).

Metoprolol
c_{effl} has a value of 4 µg/L in the study from Fick et al. (2009) and an average of 875 µg/L in the study from Larsson et al. (2007). In spite of the large discrepancy between these values, both were deemed a reliable representation of the metoprolol concentrations at the time of sampling. This is due to the fact that in both studies, other pharmaceuticals (except for ciprofloxacin) were measured in concentrations with the same order of magnitude as metoprolol. As a result, it was decided to take the arithmetic mean of these values, which led to a c_{effl} of around 440 µg/L. To assess the minimum and maximum concentration values' influence on the final GWF, they were used as input for the sensitivity analysis (refer to Appendix E). For the maximum allowed concentration (c_{max}), 62 µg/L was adopted (RIVM, 2014). Lastly, Q_{effl} is equal to the PETL WWTP effluent discharge mentioned in the previous section: 589275 m^3/year.

In cases where a link between the GWF and production quantities could not be established, the water pollution level (WPL) of the receiving water body was calculated. The WPL describes the ratio of GWF to river runoff and is calculated by dividing the GWF by river discharge.

2.4.3 GWF of global ciprofloxacin and antibiotic consumption

Alternative to the EU perspective, the global production-related environmental impact of human ciprofloxacin consumption was assessed. To achieve this, it was assumed that all ciprofloxacin products are produced with the previously calculated GWF. For the global consumption quantity, an estimate by Oldenkamp et al. (2019) was used (2318 tons in 2015). In addition, the impact of global human antibiotic consumption was examined by means of a hypothetical scenario. It was assumed that the environmental impact of ciprofloxacin manufacturing is representative for antibiotics in

[6] Since 2009, effluents from PETL WWTP are transported to Amberpet STP (refer to Section 3.3 for more information).

[7] Correction to Gothwal & Shashidhar (2016): Table 2, Fluoroquinolone concentrations were erroneously swapped for sites 6 and 7 (R. Gothwal, personal communication, November 9, 2020).

general. Accordingly, the GWF per unit of mass for antibiotic manufacturing was assumed to be equal to that of ciprofloxacin. Since antibiotic consumption data is made available in terms of the number of DDDs, the GWF per antibiotic DDD had to be calculated. The average antibiotic DDD (1.5 gram) was determined by averaging the DDDs of commonly used antibiotics (based on Amaha et al. (2020) and Sánchez-Huesca et al. (2020), which largely corresponds to the top antibiotics as mentioned by the World Health Organization (2018)). Subsequently, the GWF per antibiotic DDD was related to antibiotic consumption data for individual countries (based on World Health Organization (2018) and Klein et al. (2018)).

2.4.4 Sensitivity of the European per capita GWF

A one-at-a-time sensitivity analysis for the European production-related ciprofloxacin and metoprolol GWF was performed by changing input values of parameters c_{max}, production quantity, DDD, Q_{effl} and c_{effl}. A linear relation is present between these parameters and the final GWF. Hence, input parameters were not varied by a fixed percentage, but between plausible values derived from reports and literature. For ciprofloxacin, c_{max} was varied between the lowest PNEC for antibiotics and the PNEC for ciprofloxacin that excludes antimicrobial resistance (AMR Industry Alliance, 2018). The c_{max} thresholds of metoprolol were based on the Negligible Concentration and Maximum Acceptable Concentration for freshwater, respectively (RIVM, 2014). Minimum and maximum production quantities were based on the results of the bottom-up and top-down approach (refer to Section 2.4.1). The DDD, described by the WHO, were based on minimum and maximum DDD values. These correspond to parenteral and oral dosage forms of the two pharmaceuticals. The discharge of effluents (Q_{effl}) was derived from the Central Pollution Control Board (n.d.), which reported the influents at PETL WWTP for the years 2001 to 2011. Lastly, the minimum and maximum pharmaceutical concentrations (c_{effl}) were based on the reports from Fick et al. (2009) and Larsson et al. (2007).

3. Results

3.1 Access to information on the pharmaceutical supply chain and environmental impact

Ciprofloxacin (fluoroquinolone antibiotic) and metoprolol (β-blocker) were selected for further investigation using the criteria outlined in Chapter 2. Both are commonly used globally, as well as in a variety of European countries (based on British, Dutch, Finish and Norwegian consumption data and Seifert (2019); World Health Organization (2018)). Moreover, these pharmaceuticals are of significant importance to society, have been examined for their environmental impact, are frequently found in pharmaceutical manufacturing effluents and the number of dosage forms is limited in comparison to some other pharmaceuticals.

For the global and/or regional market analysis, a quick internet-based search for market assessment reports revealed a variety of seemingly in-depth studies. However, the companies behind these API-specific reports are producing a great number and variety of reports, and have been reported to be malicious in nature (Goldberg, 2020). Combined with the reports' hefty price tags, this approach was not deemed viable. Due to ease of contact, the public pharmaceutical data provider of the Netherlands (GIPdatabank) was contacted to obtain data on the brands and market shares of ciprofloxacin and metoprolol manufacturers and sellers in the Netherlands. They were not able to provide this due to legal reasons and a lack of resources (Zorginstituut Nederland, personal communication, July 21, 2020). Their data supplier was subsequently contacted (Stichting Farmaceutische Kengetallen (SFK)), which collects pharmaceutical consumption data from more than 98% of the public pharmacies in the Netherlands and possesses consumption data of approximately 16 million people (Stichting Farmaceutische Kengetallen, n.d.). SFK provided names of the top five marketing authorisation holders for the APIs ciprofloxacin and metoprolol[1]. Ciprofloxacin and metoprolol are both available as generic medicines, which are usually approved for market entry on a national level (European Medicines Agency, n.d.-a). As a result, it is uncertain whether the acquired organisations also hold marketing approvals for ciprofloxacin and metoprolol products in the rest of the EU. Nevertheless, since no data on the largest pharmaceutical market share holders in the EU as a whole was available, the Dutch data on top marketing authorisation holders was deemed most representative for the top marketing authorisation holders in the EU.

The marketing authorisation holders provided by SFK and other large pharmaceutical companies that have ciprofloxacin and/or metoprolol for the European market in their portfolio were contacted. The

[1] Based on: number of products sold, where a product only contains the selected API and is not a combination of multiple APIs. For both APIs, the five organisations combined possessed more than 95% of their respective market (Stichting Farmaceutische Kengetallen, personal communication, September 10, 2020).

mentioned large pharmaceutical companies[2] were selected using the Dutch database of approved pharmaceuticals (*Geneesmiddeleninformatiebank*) and DrugBank Online. In spite of this, no substantial data on (manufacturers in) the supply chain or environmental impacts could be obtained from this approach: companies either refused the request for information or did not respond. Moreover, from contact with national branches of multinationals, it was found that national branches do not seem to be familiar with the production processes and supply chain of their products.

In addition to the companies noted above, the following organisations and consortia were consulted regarding the pharmaceutical supply chain:

- The European Medicines Agency (EMA)
  The EMA performs GMP inspections and "information on the manufacturers and suppliers of the key starting materials is expected to be provided" in the EU market-authorisation application (European Medicines Agency, personal communication, September 17, 2020). This same communication also mentioned that "a list of registered manufacturers linked to Centrally Authorised Products is available at the EMA". However, that data is deemed confidential and could not be disclosed (European Medicines Agency, personal communication, September 17, 2020). In another communication, the Directorate-General for Health and Food Safety stated that no centralised database on the manufacturing chain of products authorised in the EU is available (authorised by either NCAs or the EMA). Furthermore, it was reported that "authorities will not know for an individual batch which of the declared manufacturing sites described in the MA [manufacturing-authorisation] dossier were effectively used and for which percentage of the final product supply. This information would however be available and in the batch manufacturing dossier kept by the manufacturer and could be accessed on a case by case basis, by the competent authorities, whenever needed." (European Commission, personal communication, September 8, 2020).

  Furthermore, the EMA maintains the database EudraGMDP, where regulatory authorities in the European Economic Area (EEA) share data on "manufacturing, import and wholesale-distribution authorisations, and good manufacturing-practice (GMP) and good-distribution-practice (GDP) certificates" (European Medicines Agency, n.d.-b). Although a public version of the database includes e.g. GMP certificates and general information on API manufacturers, extensive information on pharmaceutical supply chains is not available. Access to the full database was requested, but denied as "only national competent authorities can have access to the restricted part of EudraGMDP" (European Medicines Agency, personal communication, October 27, 2020).

- Authorities participating in the EMA 'Programme to rationalise international GMP inspections of active pharmaceutical ingredients/active substances manufacturers'
  This programme has the aim of improving international collaboration between regulatory authorities with regards to GMP inspections (European Medicines Agency, 2018). The reference standard for this collaboration is the harmonised ICH Q7 guideline, which largely corresponds to the guidelines as provided by the EU (ECA Academy, 2010; European Medicines Agency, 2018; ICH, 2000). The majority of the participating authorities were contacted (incl. those of Australia, Canada, the US, Japan and the WHO), but none were able to disclose information on the pharmaceutical supply chain. When a reason was cited, this was generally due to the confidential nature of the data.

  A formal Freedom of Information request was submitted to the MHRA (NCA of the United Kingdom, part of this collaboration pre-Brexit). As stated in a personal communication with the

[2] A company was considered large if it is an established and widely recognised pharmaceutical company (subjective). This is not an indication of the company's share in the European ciprofloxacin and/or metoprolol market. These additional organisations were contacted to increase the likelihood of favourable responses.

MHRA, the information was exempt from release under the following sections:

  - Section 41: Information provided to us in confidence, with the expectation that it will not be released, is exempt from disclosure under the FOI Act.
  - Section 43: Release of all, or part of, the information would, or would be likely to, cause harm to the third party's commercial interests.

The exemption was "conditional on the public interest in releasing it not outweighing the company's/commercial enterprise's right to confidentiality and the probable damage that the company/commercial enterprise could suffer as a result of the information being released.". It was declared that in this case "no issues which would benefit the public as a whole by being brought to their attention (examples of issues would be a major public health risk or a major procedural failure or irregularity)" were identified by the MHRA (MHRA, personal communication, October 16, 2020).

- The Dutch NCA: College ter Beoordeling van Geneesmiddelen
  Although the Dutch NCA does possess information on the supply chain of pharmaceutical manufacturers, it is not able to share this information due to the confidential nature of the data (College ter Beoordeling van Geneesmiddelen, personal communication, September 17, 2020).

- The Swedish NCA: Läkemedelsverket
  As mentioned by Larsson & Fick (2009), the Swedish Medical Products Agency (Swedish: Läkemedelsverket) has information on the origin of APIs and has supplied this information in the past. A formal request was submitted, which was denied with a similar argument as that from the MHRA (Swedish Medical Products Agency, personal communication, October 15, 2020). Furthermore, they could not disclose this information on the basis of confidentiality due to uncertainties in criminal liability (with respect to different judicial systems).

- Rx-360: a non-profit international pharmaceutical consortium that is involved in pharmaceutical supply chain security
  Rx-360 agreed to distribute a survey on the European pharmaceutical supply chain among their members, who are active in all stages of the pharmaceutical supply chain. Of the 52 respondents, most were active in FPP manufacturing, followed by API production, suppliers of other ingredients and contract manufacturers. Over 80% produced for the European market. Although only a few respondents made products related to ciprofloxacin, Germany was the most common production location. When asked where primary (API) and secondary (FPP) manufacturing for the European market was most commonly taking place, China, Germany and India were the top choices for API production. For FPPs, the US, Germany and the EU were most often mentioned[3].

- Hovione: a pharmaceutical manufacturer
  A respondent to the Rx360 survey, they proposed to give more insights into the pharmaceutical supply chain. As described by G. Villax, CEO of Hovione, the pharmaceutical supply chain is extremely diverse and fragmented: individual companies only have small market shares in an industry that reaches around 1 trillion USD of global revenue per year (prescription medicines) (G. Villax, personal communication, November 25, 2020). Although the complexity and extent of the manufacturing process and supply chain varies between pharmaceuticals, generally, many partners are involved. Raw materials are used to produce intermediates, which are subsequently used to manufacture APIs. Intermediates can be common to multiple products and APIs can be used as a basis for other APIs. Subsequently, these products are processed into FPPs, which can require many mechanical and chemical steps as well (G. Villax, personal communication, November 25, 2020). The above illustrates that there is no small set of manufacturers in the

[3] In the survey, no distinction was made between generic and branded pharmaceuticals.

pharmaceutical supply chain, but that environmental pollution can occur in all the different stages and manufacturing locations.

Ultimately, results demonstrate that detailed information on the pharmaceutical supply chain and its environmental impacts cannot be obtained by the consumer or the scientific community (the same holds when confidentiality regarding the source is assured). No substantial data on the supply chain and environmental impact of pharmaceutical manufacturers was obtained through publicly accessible data. Neither was this obtained by contact with marketing authorisation holders, governmental bodies or intergovernmental organisations. With the exception of the few organisations that shared information, this affirms the scientific community's view on the lack of transparency in the pharmaceutical supply chain (Larsson & Fick, 2009; Stenuick et al., 2020). Contact with a pharmaceutical consortium and a manufacturer did demonstrate that the pharmaceutical supply chain is complex, extensive and involves many different parties. Manufacturing for the EU seems to take place in the EU itself, but also in other regions: manufacturing of APIs is more likely to be outsourced to China and India, whereas production of FPPs mainly occurs in the EU and US.

3.2 Pharmaceutical supply chain for the European market

To gain an understanding of the pharmaceutical supply chain without information from marketing authorisation holders or legislative bodies, trade data was used. As mentioned in the previous section, the pharmaceutical supply chain is complex in nature: To get to an API or FPP, a considerable amount of intermediate steps and products are required. Since only trade of products associated with APIs and FPPs could be described with HS codes (as opposed to raw materials, intermediates or other starting materials; refer to Section 2.3), this section does not provide a complete picture of the supply chain. In this study, the term 'studied products/APIs/FPPs' refers to products in the respective HS categories, which include but are not limited to ciprofloxacin and metoprolol APIs or FPPs

Figures 4 and 5 show trade data with respect to FPPs, Figure 6 shows trade data with respect to APIs. For retail[4] and non-retail[5] sale, the EU, China, India and the US are big exporters of the studied FPPs. Combining both trade flows, Germany shows the largest export with a share of almost 15% of total export. It is followed by France, India and China, which all account for 7% of total export. It is interesting to note that export from Mexico to the US, with a share of almost 3% of total trade, is largest of all country to country trade flows. It is followed by trade from India to the US (2%), Ireland to Belgium/Luxembourg (2%) and the US to Canada (1%).

[4]Medicaments for retail sale or put in measured doses. These are pharmaceuticals in their final dosage form, such as tablets or capsules ready for retail sale (Tax and Customs Administration of the Netherlands, personal communication, December 12, 2020).

[5]Medicaments not for retail sale or put in measured doses. These are pharmaceuticals not in their final dosage form or not ready for retail sale, such as pharmaceuticals in large containers or canisters (Tax and Customs Administration of the Netherlands, personal communication, December 12, 2020).

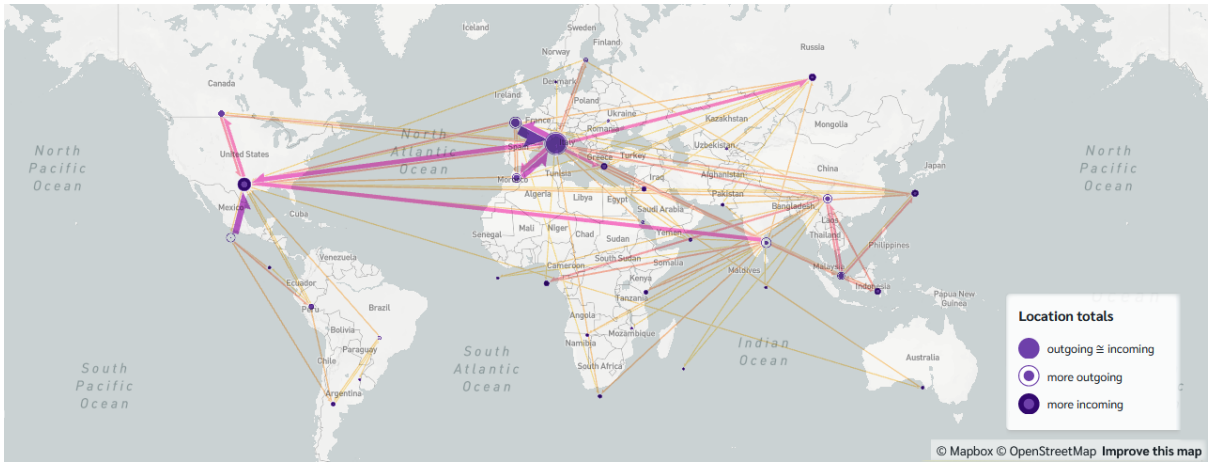

Figure 4: Top 250 FPP trade flows in 2018 by quantity (tons) for HS categories that include ciprofloxacin and metoprolol products for retail sale (HS codes 300420 and 300490, data source: BACI by CEPII (Gaulier & Zignago, 2008)), visualisation tool: Flowmap.blue (Boyandin, 2020))

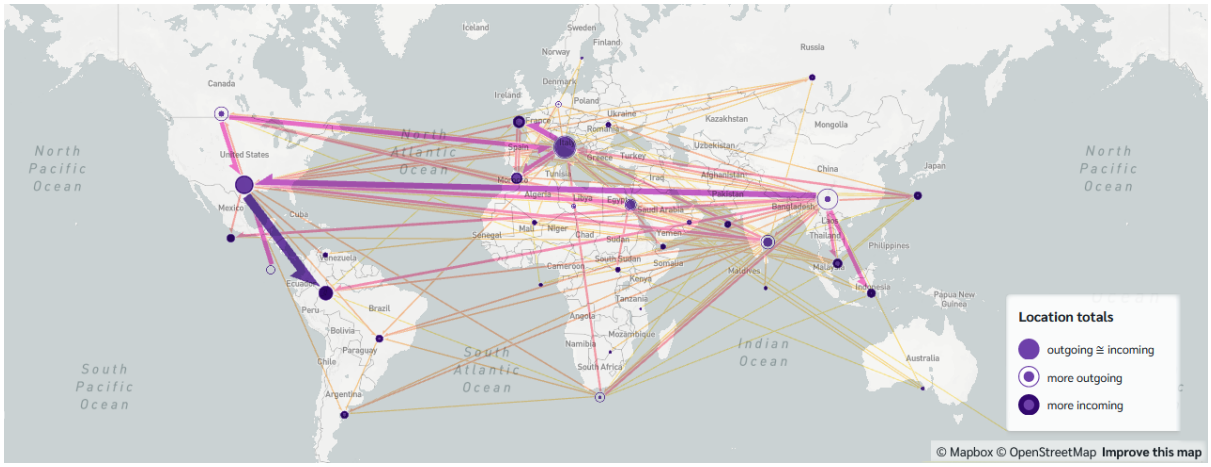

Figure 5: Top 250 FPP trade flows in 2018 by quantity (tons) for HS categories that include ciprofloxacin and metoprolol products not in measured doses (HS codes 300320 and 300390, data source: BACI by CEPII (Gaulier & Zignago, 2008)), visualisation tool: Flowmap.blue (Boyandin, 2020))

Large exporters of the studied APIs are China, Germany and the US with shares of 30, 17 and 16%, respectively. China exports substantial quantities to India, with a trade flow accounting for almost 4% of all country to country trade. This also seems to hold for the ciprofloxacin (hydrochloride) API, as indicated by an Indian anti-dumping investigation related to Chinese producers (Ministry of Commerce & Industry, 2020). Furthermore, it is corroborated by Indian trade data on ciprofloxacin (refer to Figure 16 & 17 in Appendix B). This is not to say that India does not produce and/or export APIs, as India's share of the studied API exports is more than 3% (demonstrated for ciprofloxacin in Figure 18, Appendix B). Two other points are of interest: First, substantial trade occurs from China to Vietnam (almost 3%), which suggests that Vietnam also plays a big role in the pharmaceutical supply chain. Second, Sweden accounts for more than 3% of API export, but only exports to 39 partners. Spain, on the other hand, is responsible for (only) 1% of API export, but has more than 2.5 times the trading partners than Sweden.

Reflected by Figure 6, the studied APIs are mainly imported by the US (10%), the EU (Germany: 8%, UK: 6%), China (7%) and India (6%). A possible conclusion from these observations is that China is a

big producer of the studied APIs, which are then used for further production in the country itself, in India, in the US or in the EU. The fact that APIs are further processed in the EU is substantiated by the bulk of package inserts of FPPs sold in the EU and personal communication with AstraZeneca. When APIs are processed into FPPs by China or India, the end products are subsequently imported by other countries, such as those in the EU (refer to Figures 4 and 5). This is substantiated by trade data from India for the processed pharmaceuticals ciprofloxacin (HS 30042013 & HS 30042033) and metoprolol (HS 30049074) (refer to Figures 13 and 15 in Appendix B). An interesting observation is that India seems to export final ciprofloxacin products on a large scale to Russia, which is not directly evident from Figure 4. However, this is likely due to the coarser aggregation of Figure 4, as the same aggregation level on the Indian trade portal shows similar results as Figure 4 (refer to Figure 14 in Appendix B).

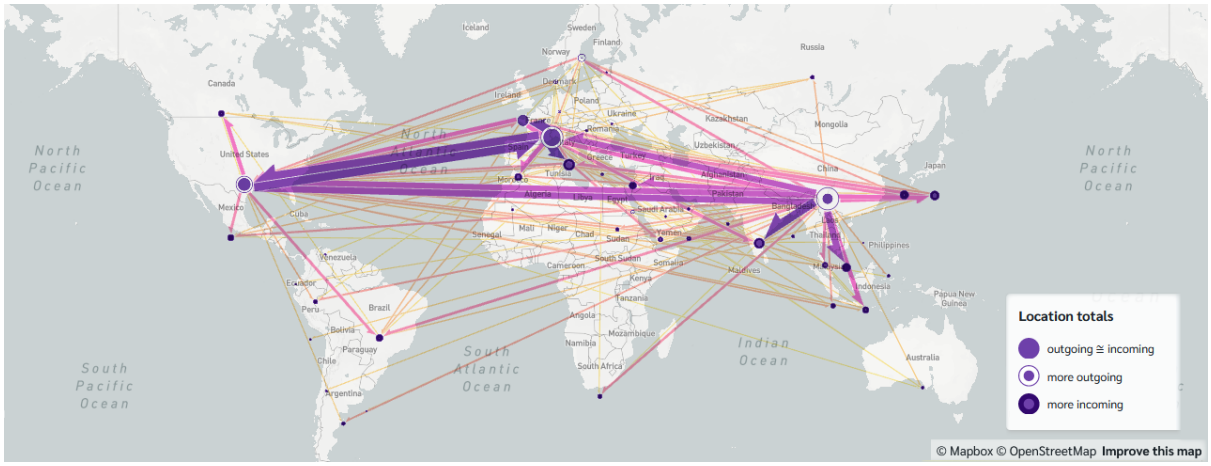

Figure 6: Top 250 API trade flows in 2018 by quantity (tons) for HS categories that include the APIs related to ciprofloxacin and metoprolol (e.g. including ciprofloxacin hydrochloride) (HS codes 292219, 293359 and 294190, data source: BACI by CEPII (Gaulier & Zignago, 2008)), visualisation tool: Flowmap.blue (Boyandin, 2020))

When the countries' balance of trade for the studied HS codes is assessed, it becomes evident that most export can be attributed to a selection of countries. Figure 7 demonstrates that the EU, China and India are large exporters of the studied products, whereas the US and Russia are big importers.

Figure 7: Countries' balance of trade for HS categories that include ciprofloxacin and metoprolol APIs and FPPs. Red signifies net export and blue net import. (HS codes 292219, 293359, 294190, 300320, 300390, 300420 and 300490, data source: BACI by CEPII (Gaulier & Zignago, 2008)), visualisation tool: Flowmap.blue (Boyandin, 2020))

3.3 The GWF of pharmaceutical manufacturing

The production-related GWF was quantified for pharmaceutical companies supplying wastewater to PETL WWTP in Hyderabad (India) based on studies from 2007 and 2009[6]. The present situation and more context on the extent of pharmaceutical pollution is illustrated using studies of 2016 and 2017[7].

3.3.1 Background on the study area: Patancheru, India

PETL WWTP, established in 1994, is a common effluent treatment plant that treats effluents from the industrial area (incl. pharmaceutical manufacturers) in Patancheru (Hyderabad, India). To achieve the desired effluent and environmental quality standards, the plant and the supplying industries have undergone a number of measures (Central Pollution Control Board, n.d.). In 1997, a public interest petition resulted in a zero liquid discharge scheme for industries generating more than 25 m^3 effluent per day (Centre for Environment and Development et al., 2014; Changing Markets & Ecostorm, 2016). In spite of this measure, there have been reports of companies illegitimately sending their (low-TDS) effluents to PETL WWTP (Das, 2015). In 2009, a variety of measures were implemented at PETL WWTP, which did seem to improve the effluent water quality (Central Pollution Control Board, n.d.). This is substantiated by a 2018 monitoring report on PETL effluents (N.R. Donthi, personal communication, October 19, 2020). Furthermore, an 18 kilometre long pipeline was established between PETL WWTP and the Amberpet STP (Central Pollution Control Board, n.d.; Centre for Environment and Development et al., 2014; National Green Tribunal, 2017). Amberpet STP, which is supposed to further treat the PETL WWTP effluents, is reported to be ill equipped for handling pharmaceutical effluents (Das, 2015). The result seems to be that pollution has now been shifted to the receiving river of the Amberpet STP: the Musi river (Das, 2015; Swedwatch, 2020). Consequently, the environmental burden of pharmaceutical manufacturing in the area stays the same.

[6] Sampling took place in 2006 and 2008, respectively.
[7] Sampling took place in 2015 and 2016, respectively.

3.3.2 Estimating production quantities

Bottom-up approach
Using the sources outlined in Appendix C, 16 relevant manufacturers or manufacturing units were found in Patancheru, Hyderabad. Manufacturers were deemed relevant if production quantities of ciprofloxacin and/or metoprolol could be estimated and if they could be linked to the PETL WWTP. Most of the production quantities and EU export licenses were obtained through the public database of the Indian Ministry of Environment Forest and Climate Change (2020b). Note that 1) this database is not complete, 2) information on the relevant manufacturers is scarce, 3) a distinction between production for human and/or veterinary use was not possible, 4) a distinction between API and FPP manufacturing was neither possible and 4) the assumption was made that production quantities have remained constant in the past 15 years. Furthermore, Changing Markets & Ecostorm (2016) refers to an an analysis of the Telangana State Pollution Control Board, which describes that companies operating in the region are producing ingredients for which they have no permission (as well as violating other rules). This means that the accuracy and representativity of the analysed data is uncertain.

Keeping the limits of the obtained data in mind, ciprofloxacin API and FPP manufacturing was approximated at 2661 tons per year. This is in the same order of magnitude as an estimate by Cox (2007), who describes that 35 to 40% of India's bulk production takes place in Patancheru[8]. Metoprolol production was estimated to be 954 tons per year, based on licenses for metoprolol succinate and metoprolol tartrate. Although not all the manufacturers showed valid European export licenses, they are all located in the Patancheru region and are assumed to supply wastewater to PETL WWTP. Therefore, pollution cannot be attributed to a specific set of manufacturers (refer to Supplementary material S1 for data and calculations).

Top-down approach
Detailed calculations regarding the top-down approach are depicted in Appendix D.2. For ciprofloxacin APIs and FPPs, a production quantity of 926 tons per year was obtained. The production quantity for metoprolol FPPs was approximated at 1156 tons per year (metoprolol API HS codes could not be found). For metoprolol, the used 8-digit HS code also includes propranolol, atenolol and labetalol. Using Dutch, Norwegian and Finnish consumption data, the share of metoprolol was estimated to be 80%, which translates to 939 tons per year (refer to Supplementary material S1). The production volumes of metoprolol and ciprofloxacin are in the same order of magnitude as those reported in the bottom-up approach.

3.3.3 Quantification of the GWF

For both ciprofloxacin and metoprolol, the final production volumes were obtained by averaging the results from the top-down and bottom-up approaches. This has led to 1793 and 947 tons per year, respectively.

Ciprofloxacin
A ciprofloxacin GWF of 200.3 billion m^3/year was obtained for PETL WWTP in 2007/2008. Given a production volume of 1793 tons per year and a DDD of 0.9 gram (average of DDDs as mentioned by WHOCC (2019a)), this resulted in a GWF of approximately 101 m^3/DDD. When translated to the EU[9], a GWF of 18.8 m^3/capita/year was obtained. For the Netherlands and Germany, it resulted in a per

[8]Indian production of the API ciprofloxacin hydrochloride was approximately 3000 tons in 2015, 2016 and 2017 (Ministry of Commerce & Industry, 2020).

[9]The average of the Dutch, Germany, Norwegian and Finnish GWFs.

capita GWF of 18.9 and 28.1 m^3/year, respectively.

In the study by Gothwal & Shashidhar (2016), sampling was performed at the inlet and outlet of the Amberpet STP. Despite the direct connection between PETL WWTP and Amberpet STP, the concentrations could not be linked to PETL WWTP: At least one other pharmaceutical effluent treatment plant also seems to discharge effluent to Amberpet STP (Jeedimetla Effluent Treatment Limited, 2020). Consequently, a GWF for European consumption could not be established for 2016/2017. In view of this, the water pollution level (WPL) of the receiving Musi river was calculated. According to CSIR & NEERI (2019), the capacity of the Amberpet STP is 339000 m^3/day, which was assumed to be equal to its outflow (contact was made with the Amberpet STP for more exact figures, but no response was obtained). Musi river discharge was approximated to be 20 m^3/s, based on flow measurements from January 2007 to May 2008 (Amerasinghe et al., 2015). This led to a WPL of around 850: pharmaceutical pollution needs to be reduced by a factor of 850 for the river to adequately assimilate the pollutants present in the effluents of Amberpet STP. Moreover, in the river upstream of Amberpet STP and before the effluent enters the river, a ciprofloxacin concentration of 5528.9 µg/L was measured by Gothwal & Shashidhar (2016), which is more than 86 000 times the PNEC of 0.064 µg/L. Downstream of Amberpet STP, ciprofloxacin concentrations of 1999.6 µg/L and 44.7 µg/L were found by Gothwal & Shashidhar (2016) and Lübbert et al. (2017), respectively. This is 700 to 30 000 times the PNEC. To conclude, pharmaceutical pollution seems to be a problem in the entire Hyderabad region, although the severity is dependent on sampling locations.

Metoprolol
In the case of metoprolol, a GWF of around 4.2 million m^3/year was obtained for PETL WWTP in 2007/2008. With a DDD of 0.15 gram (WHOCC, 2019b), this led to a GWF of approximately 0.00066 m^3/DDD. The resulting per capita GWF for the EU is 0.0055 m^3/year. For Germany and the Netherlands, the per capita GWF comes to 0.0071 and 0.0063 m^3/year, respectively.

3.3.4 GWF of global ciprofloxacin and antibiotic consumption

A calculation of the global production-related environmental impact of human ciprofloxacin consumption resulted in a total GWF of 259 billion m^3/year for 2015, which translates to a per capita GWF of 35 m^3/year. In addition, Figures 8 and 9 illustrate the impact of antibiotic manufacturing for the global market (based on the ciprofloxacin production-related GWF).

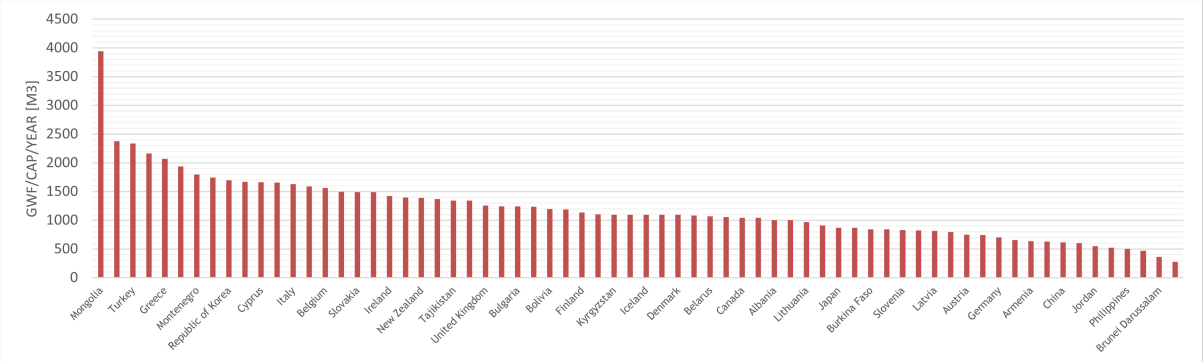

Figure 8: The yearly per capita production-related GWF of antibiotic consumption

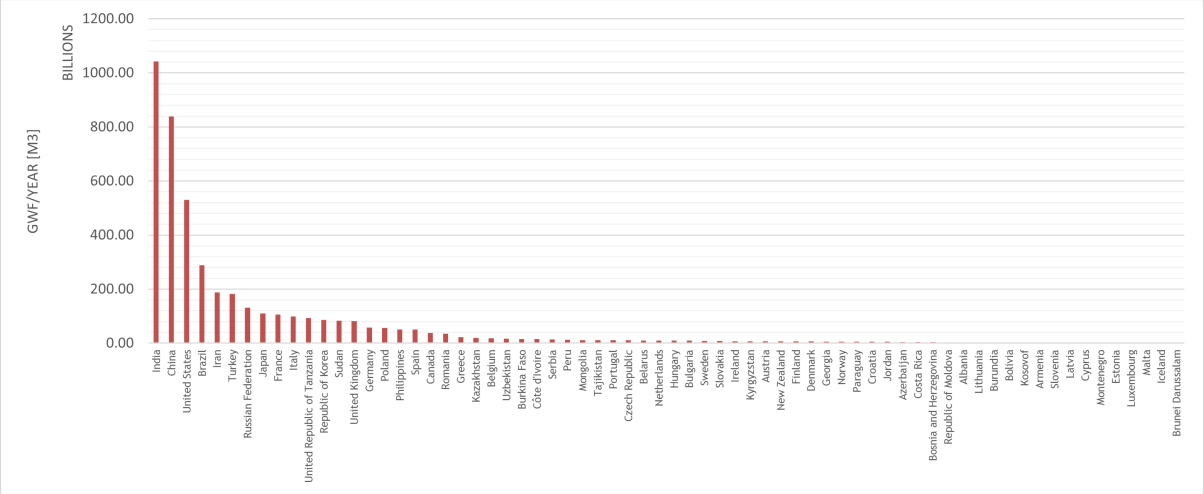

Figure 9: The yearly production-related GWF of antibiotic consumption

Mongolia shows the largest GWF per capita, which is almost 4000 m^3/year. The average per capita GWF for the manufacturing of antibiotics is approximately 1200 m^3/year. Figure 9 shows that India, China and the US are responsible for the largest GWF. Given their respective population sizes, this seems logical. Other large contributors are Iran and Turkey, which are among the leading in terms of per capita GWF. Globally, the antibiotic GWF due to manufacturing comes to approximately 4.5 trillion m^3/year, with an average of 66 billion m^3/year per country.

3.3.5 Sensitivity of the European per capita GWF

To assess how changes in input parameters affect the EU GWF, a sensitivity analysis was performed (refer to Appendix E). It is concluded that the production-related GWF is most sensitive to the maximum allowable concentration (c_{max}), which gives a EU per capita GWF range of 2.7 to 120.4 m^3/year for ciprofloxacin. This conclusion regarding c_{max} is similar to findings from Wöhler, Niebaum, et al. (2020): There is no established standard for each pharmaceutical substance and quality standards are dependent on the context in which they are devised. The same conclusion holds for metoprolol, for which the EU per capita GWF ranges from 0.0004 to 0.55 m^3/year. In all cases, the GWF for metoprolol is substantially lower than for ciprofloxacin. This can mainly be attributed to metoprolol's higher PNEC value and lower concentrations in manufacturing effluents.

4. Discussion

The aim of this research was to quantify environmental pollution caused by pharmaceutical manufacturing. This was done by investigating and describing the pharmaceutical supply chain and calculating the GWF in a specific manufacturing hotspot. The study shows that public access to pharmaceutical supply information is extremely limited. Manufacturers, governmental and intergovernmental are not willing or allowed to share data, which makes it impossible for researchers, consumers and policy makers to understand the full extent of the pollution problem. Visualising the pharmaceutical supply chains using trade data indicates that the EU is an important producer of the studied APIs and FPPs, but also imports a substantial amount from countries like India and China. For one of the manufacturing hotspots in India, it has been shown that pollution levels and consequently the GWF differ greatly between pharmaceuticals. Ciprofloxacin was found in a ten to hundred times higher concentration, but also has a lower maximum allowed concentration than metoprolol. The used environmental quality standard of ciprofloxacin is among the lowest when compared to other pharmaceuticals (Bengtsson-Palme & Larsson, 2016; Fick et al., 2010; Grung et al., 2008; Jones et al., 2002). Moreover, ciprofloxacin is one of the most common pharmaceuticals to be detected in manufacturing effluents. With this in mind, ciprofloxacin is assumed to be a suitable indicator for the most pollutive pharmaceuticals. Consequently, the antibiotic GWF, which was based on the ciprofloxacin GWF, is likely to be on the high end.

4.1 The production-related GWF in context

The per capita production-related GWF from ciprofloxacin, based on a study area in India, was estimated to be 18.8 m^3/year for the average consumer in the EU, 18.9 m^3/year for the Netherlands, 28.1 m^3/year for Germany and 35 m^3/year globally. This is only a fraction of the per capita GWF of ciprofloxacin usage, which has been estimated to be around 795 m^3/year for the Netherlands, 949 m^3/year for Germany and 1900 m^3/year globally (Wöhler, Niebaum, et al., 2020). For metoprolol, the per capita production-related GWF is 0.0063 m^3/year for the Netherlands, 0.0071 m^3/year for Germany and 0.0055 m^3/year for the EU. Again, this is substantially lower than the Dutch and German per capita GWF from metoprolol consumption of 35 m^3/year and 39 m^3/year, respectively (Wöhler, Niebaum, et al., 2020). This indicates that the manufacturing share of the investigated pharmaceuticals' GWF varies from 0 to 3%, which can be considered relatively minor. For antibiotic consumption, a production-related GWF of 1200 m^3/year was calculated for the average global consumer (based on the ciprofloxacin GWF).

Hoekstra & Mekonnen (2012) quantified the total global average per capita water footprint, which resulted in 1385 m^3/year. This includes the blue, grey and green water footprint, of which the GWF holds a share of 15%[1]. A comparison between the total water footprint and the pharmaceutical GWFs

[1]The GWF of industrial production was calculated by assessing consumptive and return flows. The return flow of industrial production was estimated as 95% of the total withdrawn water. From this return flow, the GWF was taken as

calculated and referred to in this study indicates that by including pharmaceuticals in the total GWF, a substantial increase in the total water footprint is to be expected.

4.2 Limitations of this study

There are a number of limitations to this research. First and foremost, only two pharmaceutical APIs were considered. Although attention was given to the selection of representative substances, it is no guarantee that results translate to other (generic or branded) pharmaceuticals or combinations of pharmaceuticals. The study specifically focused on pharmaceuticals for human consumption, although both are also used for veterinary purposes. Second, the lack of accurate data on supply chains and manufacturers made assessment of pharmaceutical export to the European market difficult. Supply chains were visualised using 6-digit HS code data, which are aggregates of a great number of (pharmaceutical) substances (possibly both generic and branded). They do not, however, cover raw materials or intermediates used in the manufacturing process. Therefore, conclusions on the supply chains may not cover the whole supply chain nor are they directly applicable to ciprofloxacin, metoprolol or any other single FPP or API.

Third, the GWFs calculated in this report were based on API concentrations in effluents as the sole water quality indicator. Emissions of intermediates, excipients, or byproducts were not considered. The same holds for metabolites, transformation products or mixtures of compounds, despite being potentially more toxic than parent- or single compounds (European Commission, 2015; Yin et al., 2017). Other water quality indicators such as chemical oxygen demand, total dissolved solids, temperature or the chemical's persistence in the environment were not taken into account, nor were manufacturing stages such as formulation of starting materials and intermediates considered. Lastly, API concentrations in PETL WWTP effluents were based on two studies, in which sampling was performed during limited time frames. It is uncertain to what extent the measured concentrations are representative for the average concentrations in the effluents, since companies might operate as multipurpose plants that vary the pharmaceuticals they produce (Shah, 2004).

Fourth, the GWF of pharmaceutical manufacturing has been quantified using limited information on the situation in Patancheru, Hyderabad (India). The two approaches used for estimating production quantities were in the same order of magnitude, which has increased the reliability of the results. Nevertheless, incomplete and potentially skewed information on manufacturers, production quantities, pharmaceutical trade, disposal of wastewater and European export licenses was used for this. Moreover, pharmaceutical production quantities are estimated to have been constant in the past two decades in Patancheru. In a report by Oldenkamp et al. (2019), global human ciprofloxacin consumption was estimated to be 2318 tons in 2015. This would suggest that the estimated production quantity in Patancheru (1793 tons per year) is on the high end. While it is possible that three-quarters of ciprofloxacin production occurs in the study area, the estimated quantities might not be an accurate reflection of API and FPP production for (human) consumption. For example, part of production may be intended for the veterinary sector or there has been a misinterpretation of trade data and export/production licenses.

the share that is returned without prior treatment. In these calculations, pharmaceutical concentrations were not used as indicators.

4.3 Representativity and reliability

The trade analysis shows that the EU remains a large exporter of pharmaceutical products, implying that it still a substantial producer. Wöhler, Hoekstra, et al. (2020) note that European wide pharmaceutical environmental limits are lacking, but they are established dependent on the local context and environmental inspections are subsequently performed. In addition, they referred to an interviewee active in the pharmaceutical industry, healthcare or agricultural sector who argued that pharmaceutical production would ideally move to the EU due to its stricter environmental requirements (Wöhler, Hoekstra, et al., 2020). Branded pharmaceuticals are also commonly produced in the EU and the US (Bengtsson-Palme et al., 2018); Since branded pharmaceuticals and APIs are generally more expensive than generic variants, it makes recovery of residues from wastewater (and consequently treatment) more attractive. Nevertheless, there have been reports of pharmaceutical residues in the effluents of the European pharmaceutical industry or wastewater treatment plants serving them (Anliker et al., 2020; Bielen et al., 2017). One pharmaceutical manufacturer commented that within the EU's borders, the approach towards enforcement differs between regulatory bodies and countries (G. Villax, personal communication, November 25, 2020). This, in turn, can affect the willingness of parties to cooperate and work towards a common goal, such as minimisation of the environmental burden. Ultimately, it is uncertain to what extent the calculated GWFs represent pharmaceutical manufacturing in European countries or, for that matter, regions outside of Patancheru, India.

The sensitivity analysis shows that parameters used in the GWF calculation come with considerable uncertainty. An interesting observation is that c_{max} seems to have a larger uncertainty for metoprolol than for ciprofloxacin, despite the fact that there is no risk of AMR[2]. c_{max} is also indicated as the most uncertain factor, which can be attributed to the lack of an established standard for each pharmaceutical substance. An important consideration is, however, that the accuracy of the production quantities cannot be validated; Yet, they are supported by the fact that both the top-down and bottom-up approach resulted in values with the same order of magnitude.

[2]It has been reported that non-antibiotics, including metoprolol, can inhibit growth of certain bacteria and enhance the effects of antibiotics (Akilandeswari & Ruckmani, 2015; Kruszewska et al., 2006). However, potential implications for AMR were not found.

5. Conclusion

The main outcomes of this research are compiled in Figure 10. It has been demonstrated that the supply chain is divided into a number of stages, where each stage can involve multiple intermediary products, processes and manufacturing partners. The depicted GWFs are based on the presence of the respective API in surface water or effluents and do not cover primary manufacturing stages such as formulation of raw materials and intermediates. Locations are ordered in terms of perceived share in the market and are based on the survey by Rx-360 (primary manufacturing and secondary manufacturing) and HS trade data (API and FPP trade related to ciprofloxacin and metoprolol). More elaborate conclusions are presented in the following sections.

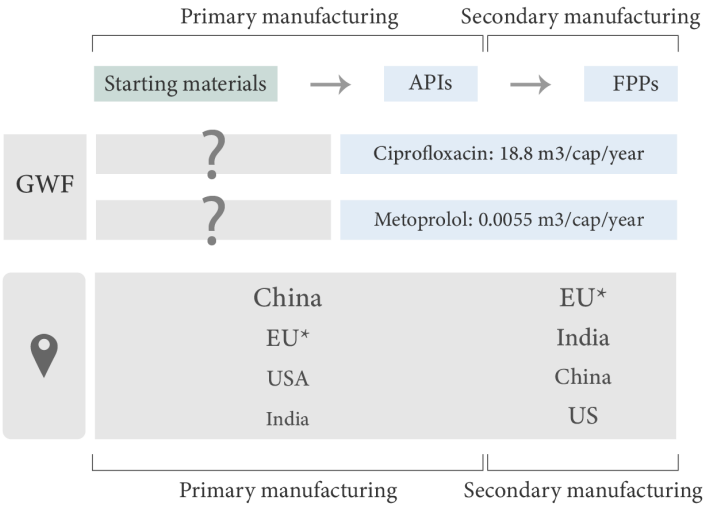

Figure 10: A coarse overview of the pharmaceutical manufacturing supply chain, its GWF and important production locations. *Within the EU, Germany plays a substantial role in terms of API and FPP export and manufacturing.

5.1 Access to information on the pharmaceutical supply chain and impact

The present study shows that extremely limited information concerning the pharmaceutical supply chain and its environmental impact is publicly available. Neither is this information made available, for publication or with a declaration regarding confidentiality, when contact is sought with pharmaceutical marketing authorisation holders, governmental and intergovernmental organisations. In this context, the right to confidentiality and the potential negative impact on pharmaceutical companies reportedly outweighs the benefit to the public. Accordingly, no substantial information on

the pharmaceutical supply chain or its environmental impact was obtained through this approach.

5.2 Pharmaceutical supply chain for the European market

Publicly available trade data, scientific literature and contact with pharmaceutical organisations show that the pharmaceutical supply chain is a complex system in which many parties are involved. Major stages are API and FPP manufacturing, but both can involve a variety of intermediary processes and partners. Pharmaceuticals for the European market are produced across the world, with big manufacturing hotspots located in the EU, China and India. Trade data indicates that Germany is a big producer of the studied FPPs, with its export accounting for almost 15% of total trade in the selected pharmaceutical categories. China seems to produce the largest part of the studied APIs, as it accounts for 30% of total export in relevant trade categories. In the context of the EU, manufacturers that export to the EU need to adhere to rules and regulations governing pharmaceuticals for the European market, irrespective of where the manufacturer is based. However, these rules and regulations do not cover environmental emissions. This makes environmental stewardship dependent on the local regulatory context and the ambitions of the manufacturer.

5.3 Production-related GWF and its relation to the European consumer

The production-related GWF was assessed for a manufacturing hotspot located in Patancheru, India. Pharmaceutical concentrations in the environment were found to be up to 86 000 times higher than the environmental quality standard. Evaluating the GWF of ciprofloxacin and metoprolol produced in this area resulted in their respective per capita GWF of 18.8 and 0.0055 m^3 per year for the European consumer. Translated to global antibiotic consumption, an average per capita GWF of 1200 m^3/year was estimated. Although the manufacturing stage only represents 0-3% of the total pharmaceutical GWF for ciprofloxacin and metoprolol, loads are concentrated at production locations; thus, local environmental impacts are potentially substantial. Consequently, indirect impacts are on a global level, with the promotion of antimicrobial resistance as the most notable example. In respect to a consumer's average total water footprint, a substantial increase is expected when the pharmaceutical GWF is incorporated.

5.4 Relation to current situation

Globally, increasing attention is given to pharmaceuticals in the environment. Examples are the EU Strategic Approach to Pharmaceuticals in the Environment and the WHO's plan to include environmental criteria in its GMP (European Commission, 2019b; World Health Organization, 2019). In these approaches, the role of the consumer is often underrepresented. As stated by Larsson & Fick (2009), the consumer can put substantial pressure on manufacturers, driving them to improve conditions. This study has highlighted the lack of transparency in the pharmaceutical supply chain and the severity of pharmaceutical pollution in a specific manufacturing hotspot. The lack of transparency limits the consumer's ability to make informed choices regarding their pharmaceutical consumption, nor do manufacturers feel obliged to justify their environmental impact to society. This is reinforced by the fact that governmental and intergovernmental bodies do not share this information either. The need to address this lack of transparency has already been expressed by the scientific community on a number of occasions, but a change in status quo is yet to come. In spite of the lack of information, the pharma-

ceutical supply chain seems to entail many different steps and partners and tends to be complex in nature. In this context, increasing transparency in the pharmaceutical supply chain is a challenging undertaking. Personal communication with a pharmaceutical manufacturer has suggested that, at this moment, regulation would be more effective (G. Villax, personal communication, November 25, 2020). The inclusion of environmental criteria in the regulatory framework has already been proposed by Sweden and the WHO (OECD, 2019; World Health Organization, 2019). Lastly, self-regulation has been described as a powerful tool: Pharmaceutical marketing authorisation holders or buyers can demand strict environmental standards from their suppliers and have done so in the past (G. Villax, personal communication, November 25, 2020). Norway, for example, has included environmental criteria in the pharmaceutical procurement process of antibiotics (Sykehusinnkjøp, 2019).

6. Recommendations

This study provides a first quantification of the production-related pharmaceutical GWF using ciprofloxacin and metoprolol for European consumption as substantiated examples. For future research, it is advised to consider a number of points for improving the results' accuracy and reliability. First, an increase in the number of studied substances would give a more nuanced representation of the GWF. In this case, the studied substances would ideally include both branded and generic pharmaceuticals, cover a large set of therapeutic groups and show diverse chemical and ecotoxicological properties. It follows that more data on pharmaceuticals in manufacturing effluents needs to be obtained. This data not only needs to include pharmaceutical concentrations, but also other water quality indicators. Second, it is recommended to put more focus on specific manufacturing processes and stages. This will give insights into where pollution is most likely to occur and accordingly, where action is most urgent. Third, the GWF of pharmaceutical consumption and manufacturing can be incorporated in a renewed total water footprint. This would allow it to better represent the impact of consumers on the environment and, following this, help to increase awareness and stimulate a critical view on consumption patterns.

With regards to policy, it is advised to stimulate transparency in the pharmaceutical supply chain. An increase in transparency will allow: 1) researchers to reduce uncertainties in the quantification of the pharmaceutical industry's environmental impact, 2) regulators to translate an improved understanding of the industry and its impacts into (enforceable) legislation and 3) consumers to make informed decisions regarding their consumption behaviour. To this end, the complex pharmaceutical supply chain should be made accessible and understandable for a broad public audience. On the short term, it is strongly advised to further incorporate environmental criteria in the regulatory framework with regards to pharmaceutical manufacturing and market entry.

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A. Ciprofloxacin share in HS 300420

To determine a rough share of the FPPs related to ciprofloxacin in HS group 300420, antibiotic consumption data of a variety of countries was used. Note that a different HS category is available for penicillins and streptomycins, so trading in these substances is likely to be filed under that specific category (HS 300410). However, as only a rough estimate was calculated, this was not taken into account. As a result, the depicted ratios will likely be on the low end.

The Netherlands
By Defined Daily Dose - 2017
Inhabitants: 17.2 million (CBS, 2018)
Total ciprofloxacin consumed: 0.56 (GIPdatabank (2017): total DDDs converted to DDDs per 1000 inhabitants per day)
Total antibiotics consumed: 10.06 (RIVM & SWAB, 2020)
Ratio of ciprofloxacin to total antibiotic consumption in terms of DDD: 6%

By mass - 2007
Total ciprofloxacin consumed: 2387 kg (van der Aa et al., 2008)
Total antibiotics consumed: 30.378 kg (van der Aa et al., 2008)
Ratio of ciprofloxacin to total antibiotic consumption in terms of mass: 8%

Norway
By Defined Daily Dose - 2017
Total ciprofloxacin consumed: 0,43 per 1000 inhabitants per day (Sakshaug et al., 2018)
Total antibiotics consumed: 17,87 per 1000 inhabitants per day (Sakshaug et al., 2018)
Ratio of ciprofloxacin to total antibiotic consumption in terms of DDD: 2%

Finland
By Defined Daily Dose - 2019
Total ciprofloxacin consumed: 0,38 per 1000 inhabitants per day (fimea, 2019)
Total antibiotics consumed: 16,85 per 1000 inhabitants per day (fimea, 2019)
Ratio of ciprofloxacin to total antibiotic consumption in terms of DDD: 2%

China
By mass - 2013
Total ciprofloxacin consumed: 455 tons (Zhang et al., 2015)
Total antibiotics consumed: 77760 tons (Zhang et al., 2015)
Ratio of ciprofloxacin to total antibiotic consumption in terms of mass: 1%

B. Trade flows

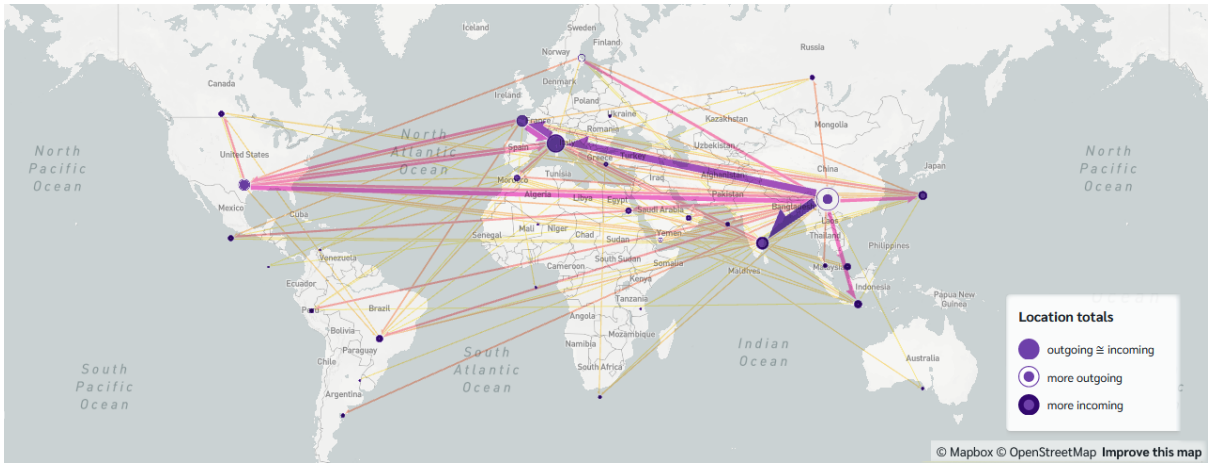

Figure 11: Top 250 trade flows in 2018 by quantity (tons) for HS codes 293359 and 294190 (data source: BACI by CEPII (Gaulier & Zignago, 2008)), visualisation tool: Flowmap.blue (Boyandin, 2020)

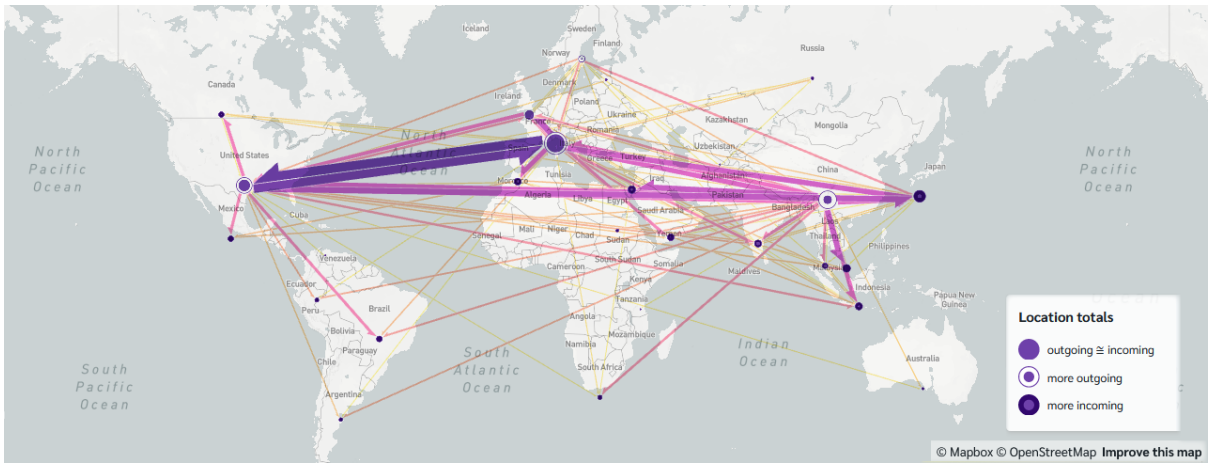

Figure 12: Top 250 trade flows in 2018 by quantity (tons) for HS code 292219 (data source: BACI by CEPII (Gaulier & Zignago, 2008)), visualisation tool: Flowmap.blue (Boyandin, 2020)

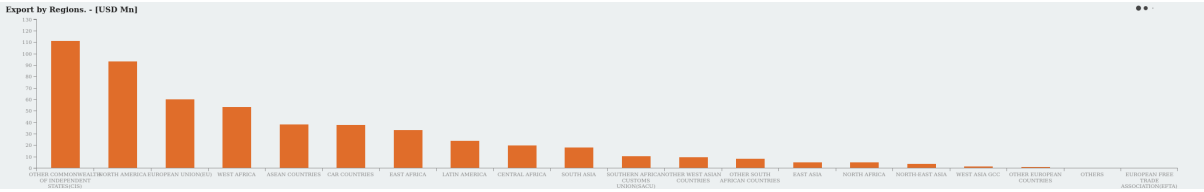

Figure 13: Indian export of “Ciprofloxacine - In capsul, tblts form etc” (HS code 30042013) & “Ciprofloxacin (Fluoroquinolones)” (HS code 30042033) in million US dollars per region from 2014 until present (DGCI&S, n.d.). Note that of the “Commonwealth of Independent States", Russia has the largest share of India’s export in these substances.

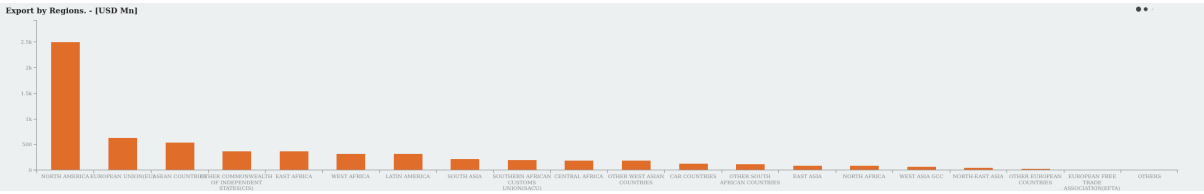

Figure 14: Indian export of overarching HS code 300420 in million US dollars per region from 2014 until present (DGCI&S, n.d.)

.

Figure 15: Indian export of “Propranolol, Metoprolol, Atenolol and Labetalol", HS code 30049074 in million US dollars per region from 2014 until present (DGCI&S, n.d.)

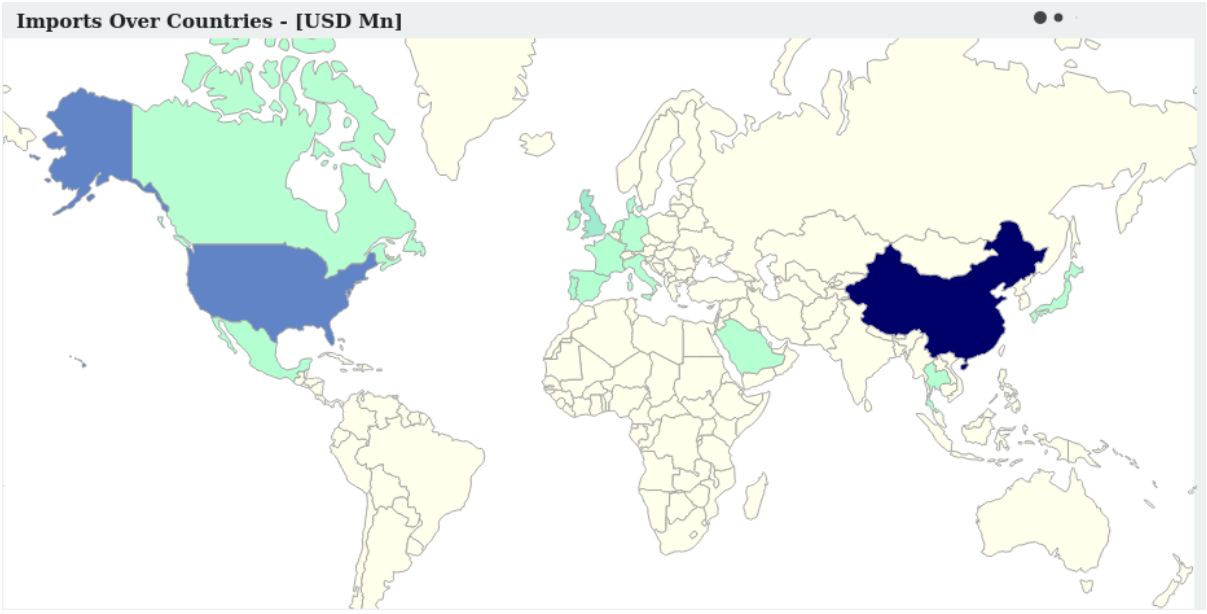

Figure 16: Indian import of “Ciprofloxacin and its salts", HS code 29419030 in million US dollars per country from 2014 until present (DGCI&S, n.d.)

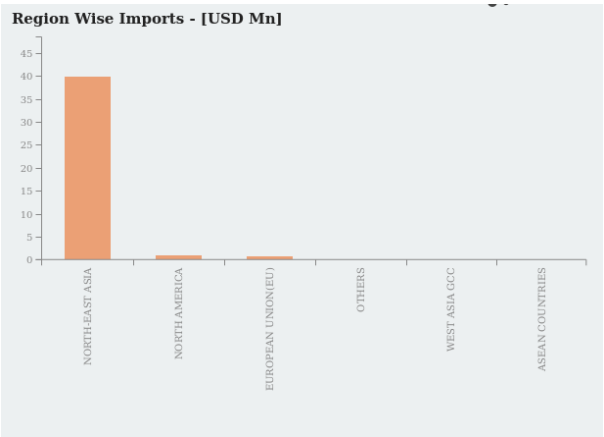

Figure 17: Indian import of “Ciprofloxacin and its salts", HS code 29419030 in million US dollars per region from 2014 until present (DGCI&S, n.d.)

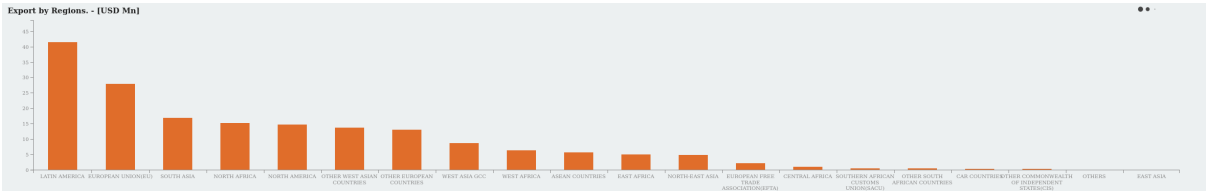

Figure 18: Indian export of “Ciprofloxacin and its salts", HS code 29419030 in million US dollars per region from 2014 until present (DGCI&S, n.d.)

C. GWF: bottom-up approach

C.1 Reviewed or contacted sources: successful approaches

Telangana State Pollution Control Board EnviroConnect
Source: Telangana State Pollution Control Board (2020)
Description: A water quality monitoring tool, which shows (part of the) companies operating in Telangana state.

Inventorisation and Characterisation of Hazardous Waste Categories in Andhra Pradesh and Telangana States
Source: Centre for Environment and Development et al. (2014)
Description: A report by various (local) organisations that, among other things, mentions pharmaceutical manufacturers operating in the region.

Preliminary Findings in the anti-dumping investigation concerning imports of "Ciprofloxacin Hydrochloride" originating in or exported from China PR
Source: Ministry of Commerce & Industry (2020)
Description: A report on the import of the API ciprofloxacin HCL from China by India. It also lists Indian importers and domestic producers of the same API.

Database of Certificates of Suitability holders from the EDQM
Source: EDQM (2020)
Description: The database holds manufacturers which have obtained a 'Certificate of Suitability', a quality control certificate, from the European Directorate for the Quality of Medicines and HealthCare (EDQM) for the manufacturing of certain pharmaceutical substances.

Action Plan for Rejuvenation of River Stretches (Priority I and II) in Telangana State
Source: CSIR & NEERI (2019)
Description: A report by governmental organisations that shows, among other points, industries withdrawing groundwater from the Manjeera Nakkavagu river stretches.

EudraGMDP database
Source: European Medicines Agency (n.d.-b)
Description: The European database that holds data on pharmaceutical manufacturers and GMP inspections. Public access is available, but full access was denied.

Contact with local researcher
Description: Contact was made with a local researcher (Dr. Narasimha Reddy Donthi) that had covered the pharmaceutical industry and/or pollution problem in the Patancheru region. This led to the

acquirement of a list of companies supplying wastewater to PETL WWTP and monitoring data of PETL WWTP effluents.

Indian monitoring and compliance reports database
Source: Ministry of Environment Forest and Climate Change (2020a)
Description: The Indian government publishes a significant amount of monitoring and compliance reports that hold data on allowed production volumes, waste management strategies and licenses to export to the EU.

Google Maps
Description: A number of manufacturers are visible on Google Maps.

C.2 Reviewed or contacted sources: unsuccessful approaches

Not all approaches were successful. In the following cases, either no response was received or they were not able to help.

- The Indian Central Drugs Standard Control Organization
- The Andra Pradesh Pollution Control Board
- The Telangana State Pollution Control Board
- The Telangana State Department of Environment, Forests, Science and Technology
- The Indian Pharmaceutical Export Promotion Council
- The Indian Directorate General of Foreign Trade
- Several Indian pharmaceutical supraorganisations (Indian Pharmaceutical Association, Indian Drug Manufacturers association & Bulk Drug Manufacturers Association)
- The Patancheru Enviro Tech Ltd. wastewater treatment plant (PETL WWTP)
- The Amberpet sewage treatment plant (Amberpet STP)

D. GWF: top-down approach

D.1 Indian export of studied pharmaceuticals

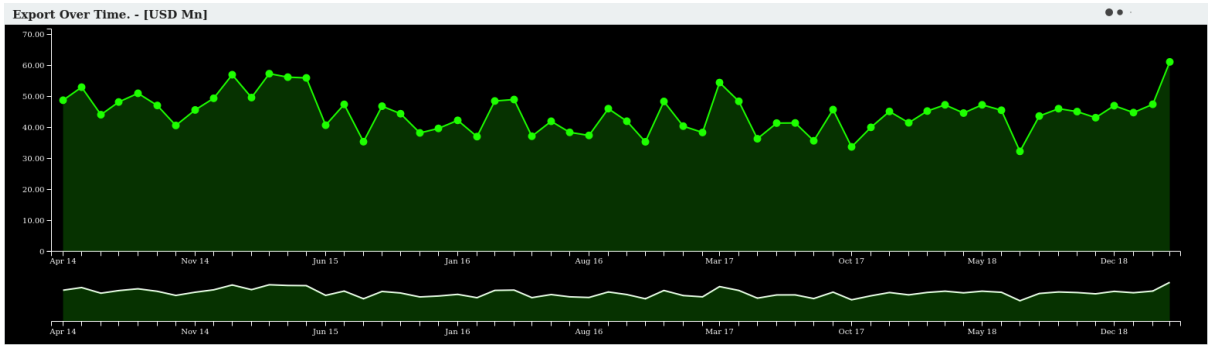

Figure 19: Indian export of HS code 294190, the overarching group of the ciprofloxacin API (HS 29419030) (DGCI&S, n.d.)

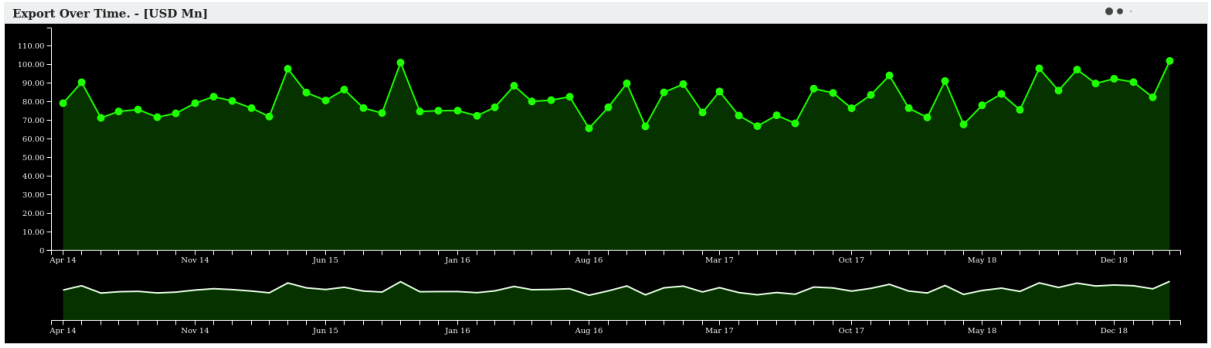

Figure 20: Indian export of HS code 300420, the overarching group of the ciprofloxacin FPP (HS 30042013 & HS 30042033) (DGCI&S, n.d.)

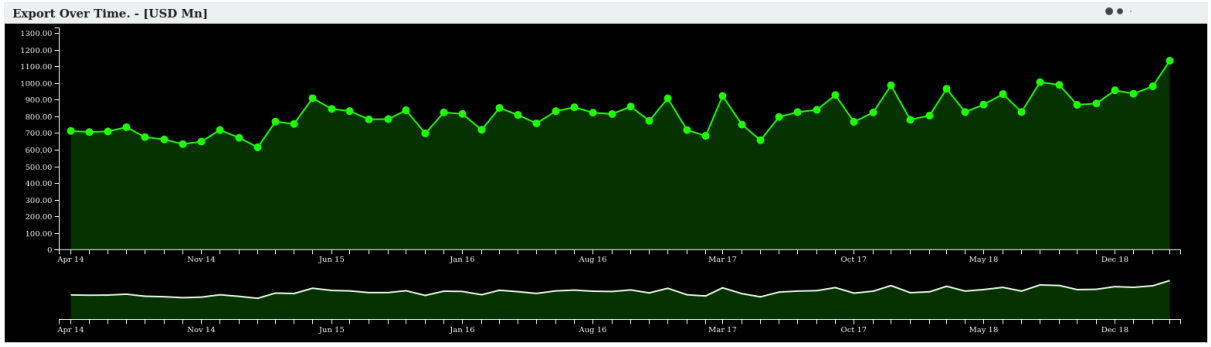

Figure 21: Indian export of HS code 300490, the overarching group of the metoprolol FPP (HS 30049074) (DGCI&S, n.d.)

D.2 Calculation of production quantity

Table 2: Calculation of European export quantity of manufacturers in the Patancheru area for ciprofloxacin (FPPs and APIs)

HS 300420			
Quantity (total export)	26994	tons	BACI 2018
Value (total export)	1039	million USD	BACI 2018
Value (total export)	1040	million USD	DGCI&S 2018
Value per unit mass	38516.6	USD/ton	[a]
HS 30042013 & 30042033			
Value (total export)	81.4	million USD	DGCI&S 2018
Quantity (total export)	2112	tons	[b]
Quantity (Patancheru export)	845	tons	[c]
HS 294190			
Quantity (total export)	4287	tons	BACI 2018
Value (total export)	519	million USD	BACI 2018
Value (total export)	547	million USD	DGCI&S 2018
Value per unit mass	124260	USD/ton	[a]
HS 29419030			
Value (total export)	25.1	million USD	DGCI&S 2018
Quantity (total export)	202	tons	[b]
Quantity (Patancheru export)	81	tons	[c]
Total quantity produced in Patancheru	926	tons	

[a] Average of BACI 2018 and DGCI&S values divided by BACI 2018 quantity
[b] Assuming uniform pricing in HS code 300420: Value (total export)/Value per unit mass
[c] Assuming 40% of bulk production takes place in Patancheru (Cox, 2007)

Table 3: Calculation of European export quantity of manufacturers in the Patancheru area for metoprolol (FPPs)

HS 300490			
Quantity (total export)	269982	tons	BACI 2018
Value (total export)	11641	million USD	BACI 2018
Value (total export)	11207	million USD	DGCI&S 2018
Value per unit mass	42313	USD/ton	[a]
HS 30049074			
Value (total export)	122	million USD	DGCI&S 2018
Quantity (total export)	2890	tons	[b]
Quantity (Patancheru export)	1156	tons	[c]
Total quantity produced in Patancheru	1156	tons	

[a] Average of BACI 2018 and DGCI&S values divided by BACI 2018 quantity
[b] Assuming uniform pricing in HS code 300490: Value (total export)/Value per unit mass
[c] Assuming 40% of bulk production takes place in Patancheru (Cox, 2007)

E. Sensitivity analysis

Table 4: Sensitivity analysis for the production-related GWF of European ciprofloxacin consumption

Parameter		Value	**GWF/cap (m3/year)**	Change
c_{max} (µg/L)	Minimum	0.010 [1a]	**120.4**	+540%
	Selected	0.064	**18.8**	
	Maximum	0.450 [1b]	**2.7**	-86%
Production quantity (ton per year)	Minimum	926 [2a]	**36.4**	+94%
	Selected	1793	**18.8**	
	Maximum	2661[2b]	**12.7**	-32%
DDD (gram)	Minimum	0.8 [3a]	**16.7**	-11%
	Selected	0.9	**18.8**	
	Maximum	1.0 [3b]	**20.9**	+11%
Q_{effl} (m3/year)	Minimum	408590 [4a]	**13.0**	-31%
	Selected	589275	**18.8**	
	Maximum	621420 [4b]	**19.8**	+5%
C_{effl} (µg/L)	Minimum	14000 [5a]	**12.1**	-36%
	Selected	21750	**18.8**	
	Maximum	31000 [5b]	**26.8**	+43 %

[1a] Lowest antibiotic PNEC (AMR Industry Alliance, 2018)
[1b] Highest environmental ciprofloxacin PNEC (excl. antimicrobial resistance) (AMR Industry Alliance, 2018)
[2a] Estimated using top-down approach (refer to Section 3.3.2)
[2b] Estimated using bottom-up approach (refer to Section 3.3.2)
[3a] Parenteral DDD of ciprofloxacin (WHOCC, 2019a)
[3b] Oral DDD of ciproloxacin (WHOCC, 2019a)
[4a] Lowest reported effluent quantity of PETL WWTP between 2001 and 2011 (Central Pollution Control Board, n.d.)
[4b] Highest reported effluent quantity of PETL WWTP between 2001 and 2011 (Central Pollution Control Board, n.d.)
[5a] Lowest measured ciprofloxacin concentration of PETL WWTP effluents (Fick et al., 2009)
[5b] Highest measured ciprofloxacin concentration of PETL WWTP effluents (Larsson et al., 2007)

Table 5: Sensitivity analysis for the production-related GWF of European metoprolol consumption

Parameter		Value	**GWF/cap (m3/year)**	Change
c_{max} (µg/L)	Minimum	0.062 [1a]	**0.5506**	+9900%
	Selected	62	**0.0055**	
	Maximum	760 [1b]	**0.0004**	-92%
Production quantity (ton per year)	Minimum	939 [2a]	**0.0056**	+1%
	Selected	947	**0.0055**	
	Maximum	954 [2b]	**0.0055**	-1%
DDD (gram)	Minimum	0.15 [3a]	**0.0055**	0%
	Selected	0.15	**0.0055**	
	Maximum	0.15 [3b]	**0.0055**	0%
Q_{effl} (m3/year)	Minimum	408590 [4a]	**0.0038**	-31%
	Selected	589275	**0.0055**	
	Maximum	621420 [4b]	**0.0058**	+5%
C_{effl} (µg/L)	Minimum	4 [5a]	**0.0001**	-99%
	Selected	440	**0.0055**	
	Maximum	950 [5b]	**0.0119**	+116 %

[1a] Negligible Concentration value for freshwater ecosystems (RIVM, 2014)
[1b] Maximum Acceptable Concentration EQS for freshwater ecosystems (RIVM, 2014)
[2a] Estimated using top-down approach (refer to Section 3.3.2)
[2b] Estimated using bottom-up approach (refer to Section 3.3.2)
[3a] Parenteral DDD of metoprolol (WHOCC, 2019b)
[3b] Oral DDD of metoprolol (WHOCC, 2019b)
[4a] Lowest reported effluent quantity of PETL WWTP between 2001 and 2011 (Central Pollution Control Board, n.d.)
[4b] Highest reported effluent quantity of PETL WWTP between 2001 and 2011 (Central Pollution Control Board, n.d.)
[5a] Lowest measured metoprolol concentration of PETL WWTP effluents (Fick et al., 2009)
[5b] Highest measured metoprolol concentration of PETL WWTP effluents (Larsson et al., 2007)