

Superbugs in the Supply Chain:

How pollution from antibiotics factories in India and China is fuelling the global rise of drug-resistant infections



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Changing Markets

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Executive Summary

Superbugs, the colloquial name for strains of bacteria which have become resistant to antibiotics, present one of the most significant global health threats of the 21st century. Every year, nearly 1 million people worldwide die from drug-resistant infections. With that figure projected to climb to 10 million by mid-century, medical experts now put drug resistance in the same bracket as the HIV/AIDS crisis, and are calling for a coordinated response from the international community to address the threat.¹

It has taken years of sustained effort to place drug resistance on the international agenda, but at long last the medical experts' pleas are beginning to reach the ears of politicians. At the G20 in Hangzhou in September 2016, world leaders acknowledged the serious danger to public health, growth and global economic stability posed by antimicrobial resistance (AMR)², a sentiment echoed at a special United Nations High-Level Meeting dedicated to the topic later on that month.³ However, despite this heightened sense of urgency, concrete action on tackling drug resistance remains slow and incomplete, and many seasoned observers fear that we are doing too little, too late.

Against this sombre backdrop, the evidence is piling up that global pharmaceutical companies – whose role it should be to cure sick people and channel resources into the development of new medicines – are actually contributing to the spread of drug-resistant infections through pollution at their own production sites or those of their suppliers. A series of recent reports⁴ have shone a light on this, the third major cause of AMR, by revealing how dirty production processes and the dumping of inadequately treated antibiotic manufacturing waste in China and India, where the lion's share of our drugs are made, is fuelling the worldwide spread of superbugs, amplifying the already considerable impact of the excessive consumption of antibiotics in human medicine and their profligate use in livestock rearing.

This report, for the first time, exposes the occurrence of resistant bacteria surrounding pharmaceutical manufacturing plants in India and maps out the supply chain which delivers antibiotics from the dirty factories where they are produced to patients in Europe and the United States. An on-the-ground investigation by the investigative agency Ecostorm which took place in June 2016 and subsequent analysis of water samples under the supervision of Dr Mark Holmes from the University of Cambridge found high levels of drug resistant bacteria at sites in three Indian cities: Hyderabad, New Delhi and Chennai.

In total, out of 34 sites tested, 16 were found to be harbouring bacteria resistant to antibiotics. At four of the sites, resistance to three major classes of antibiotics, namely the cephalosporins, carbapenems and the fluoroquinolones, was detected. At eight of the sites, resistance to cephalosporins and fluoroquinolones was detected. At a further four of the sites, resistance to either cephalosporins or fluoroquinolones was found. Of the antibiotics manufacturing plants tested, three factories respectively belonging to Aurobindo Pharma, Orchid Chemicals, and Asiatic Drugs and Pharmaceuticals, all of which supply export markets either directly or indirectly, were found to be resistance hotspots.

Detailed examination of publicly available supply chain data, and evidence obtained through Freedom of Information requests, has uncovered how antibiotics manufactured by these companies are being exported to the European and U.S. markets, including the United Kingdom's National Health Service (NHS), French hospitals, and German healthcare companies and U.S. pharma giants. Further supply chain links were also uncovered between polluting Chinese factories and Western markets.

Although probably just the tip of the iceberg, this analysis adds to the current body of knowledge on the impacts of pollution in pharmaceutical supply chains and shows that urgent action is needed to address this problem. In the current era of international travel and trade, once created, superbugs can spread quickly around the world, meaning that pollution from drug factories in India and China is not just a localised problem for people living in these areas, but could accelerate one of the biggest global health crises facing humanity this millennium.

One company in particular, Hyderabad-based Aurobindo, emerges as one of the worst offenders. A recidivist polluter at its own production sites in India, it also imports the raw materials used for making antibiotics from dirty factories in China. With strong commercial links to major players in the pharmaceutical industry, including U.S. giants McKesson and CVS Health, and an international network of subsidiaries affording direct access to Western export markets, Aurobindo has ambitions to continue expanding its global presence and market share. But at what cost to human health?

This report sends a clear message that when it comes to addressing AMR, we must address each and every one of its three causes: human, animal and industrial, or else risk losing the fight completely. With growing awareness of the gravity of the threat posed by effluent from antibiotics plants, major purchasers of antibiotics, whether publicly-owned bodies or private companies, must use their buying power to make the pharmaceutical industry clean up its act. The failure to bring manufacturing waste under control is unacceptable, presents a clear public health threat, and negatively impacts the industry's reputation as a whole. As such, this is an issue that should be of concern to pharmaceutical companies' customers, investors, and public health authorities alike.

With pharmaceutical supply chains still shrouded in mystery, purchasers should demand much more transparency on the origin of our antibiotics, requiring moves from the pharmaceutical sector mirroring those undertaken by the textiles industry in the wake of tragedies such as the Rana Plaza disaster in Bangladesh. A series of practical steps for the industry and regulators are presented at the end of this report, setting out a blueprint for best practice in a sector whose environmental performance leaves much to be desired.



Pipe discharging waste water onto beach behind Hetero Drugs' Unit IV in Rajiyapeta, near Vizakhapatnam

PART 1

Introduction

Antimicrobial resistance (AMR) arises when the microorganisms which cause infection survive exposure to a medicine that would normally kill them or stop their growth. This is a matter of particular concern in the case of antibiotics⁵. While resistance is to some extent a naturally occurring phenomenon, the increasing use of antibiotics since the second half of the 20th century, when they were first mass marketed, has created very strong selection pressure⁶ for resistant bacteria, resulting in a steep rise in untreatable infections.

Antibiotic resistance is a complex phenomenon with multiple interlinked causes. There is broad agreement that the rampant misuse of anti-infectives in both human medicine and farming are the major drivers of AMR worldwide. Many countries are taking action to address these twin factors, with varying degrees of success.

In recent years, scientific researchers have identified an additional cause of AMR: environmental pollution from the production of antibiotics⁷. Factories in China and India, which supply most of the world's antibiotics, have been revealed to be dumping waste into their surroundings, or failing to treat manufacturing discharges appropriately, resulting in the contamination of rivers and lakes and fuelling the proliferation of drug-resistant bugs.

The substantial quantities of antibiotics released from polluting factories, which frequently combine with runoff from farms and human waste in water bodies and sewage treatment plants, provide a perfect breeding ground for drug-resistant bacteria. As well as passing on resistance 'vertically' to their progeny, bacteria in these environments are able to share or exchange genetic material 'horizontally' with other bacteria, a phenomenon which can also occur between different bacterial species, including human and animal pathogens⁸.

Microbes' ability to hitch a ride on a human host or traded goods means that resistance can move quickly around the world. For instance, travellers who visit a country with high prevalence of AMR may return home colonised or infected by multidrug-resistant bacteria which can then be transmitted to others⁹. Resistance is therefore our collective problem, wherever it first occurs.

India, home to thousands of pharmaceutical manufacturing units, is a major hub of drug production. It supplies around one-fifth of the world's generic drugs¹⁰, the sale of which netted its industry \$15 billion in revenues in 2014¹¹. Anti-infectives, which include antibiotics, antivirals and antifungals, account for a substantial share of total turnover¹².

India also has a huge drug resistance problem. Nearly 60,000 newborn babies die in India each year from bacteria that are resistant to first-line antibiotics¹³. A 2015 report on the "State of the World's Antibiotics" by the Washington-based Center for Disease Dynamics, Economics and Policy (CDDEP) showed that Indian drug resistance rates for several major pathogens are on the increase. For example, for *Kebsiella pneumoniae*, a pathogen which can cause pneumonia, meningitis, bloodstream infections and urinary tract infections *inter alia*, 29 per cent were resistant in 2008, increasing to 57 per cent in 2014¹⁴.

Statistics show that antibiotic resistance is also affecting Indian livestock. Antibiotics are used in large quantities in India's intensive farming sector and, like in other countries, there are no restrictions on the use of antibiotics of critical importance to human health. The CDDEP notes that 100 per cent resistance to sulfadiazine, an antibiotic on the World

Pharmaceutical effluent floating on the surface of the Chinna Vagu River, downstream of the Patancheru-Bollaram Industrial Cluster.



View of an Aurobindo antibiotics factory (Unit XI) in Visakhapatnam, Andhra Pradesh



Health Organisation's list of essential medicines for humans, has been detected in chickens and other fowl, and resistance to the antibiotics Amikacin, Carbenicillin, Erythromycin, and Penicillin is also widespread¹⁵. In addition to causing significant economic damage to the industry and to the economy as a whole, once created, these bacteria can quickly jump species from animals to humans.

As drug resistance in India's human and animal populations continues to rise, the country's antibiotics manufacturing plants continue to pollute their surroundings. Despite decades of campaigning by local NGOs and legal action taken to the highest Indian courts, the situation on the ground has not improved. In fact, recent developments indicate that regulation targeting the pharmaceutical industry is actually becoming more lax, and pollution levels are set to rise even further, as the government lifts restrictions on plant expansion¹⁶, and introduces changes to the national pollution index (Comprehensive Environmental Pollution Index, or CEPI). This index, which has been in place since 2009, has been used to determine the environmental status of industrial areas across India, including the Patancheru Bollaram cluster featured in Part 2, which was classified as "critically polluted". The government recently removed certain criteria relating to health and the environment from the index in the name of simplification, a move criticised in media reports as being to the benefit of polluting industries¹⁷. In parallel to this, a new academic study published in September 2016, shows that antibiotic pollution remains a critical problem in Hyderabad, with concentrations of antibiotics detected in the Hyderabad area and Musi River, which flows through the city centre, 1,000 times higher than the usual concentrations found in rivers in developed countries, because of improper disposal of industrial effluent¹⁸.

China is also a major contributor to the global spread of untreatable infectious disease and a hotspot for the emergence of new microbial threats. The country suffers from high and increasing rates of antibiotic resistance: a 2012 study reported an average rise in the antibiotic resistance rate in China of 22% over 6 years, compared with 6% growth recorded for the USA over a similar time period¹⁹. Soaring drug resistance in China is driven by the incorrect use of antibiotics and strong financial incentives for prescribing them (profits from drug sales make up a large share of Chinese hospitals' income)²⁰. Excessive use of antibiotics in intensive livestock rearing and pollution from pharmaceutical manufacturing facilities²¹ are also major problems resulting in the proliferation of drug-resistant bacteria.

“Nearly a dozen current and former officials from companies producing medicines in Patancheru told Reuters that factory staff from various firms often illegally dump untreated chemical effluent into boreholes inside plants, or even directly into local water bodies at night.”

Reuters, 29 September 2016, The cost of cheap drugs? Toxic Indian lake is 'superbug hotspot'.

In late 2015, a study published in the Lancet Journal of Infectious Diseases²² revealed the discovery of a new antibiotic resistance gene in China, mcr-1 which confers resistance to Polymyxins - a class of antibiotics of last resort (antibiotics used to treat multi-drug resistant infections) that includes the drug Colistin and is widely used in livestock farming. Eight of the top ten manufacturers of Colistin are Chinese companies²³. Mcr-1 has since been found in multiple countries around the world²⁴.

With research consistently exposing severe pharmaceutical pollution problems and high levels of AMR in India and China, it is clear that a perfect storm is brewing. While the impact on local communities is all too plain to see, the antibiotic pollution crisis is a matter of significant concern to the entire international community owing to the communicability of the AMR threat, and the speed with which resistant bacteria spread around the world.

PLANT AGRICULTURE

In contaminated areas, water containing antibiotic residues and drug resistant bacteria can be absorbed into food products through cropland irrigation. In addition, croplands are often treated with antibiotic-rich manure (from medicated animals) to improve plant growth. There is also evidence that untreated solid waste from the antibiotics manufacturing process is being used as fertiliser in China. This can result in antibiotics ending up directly in the food we eat, or being washed into rivers via run-off.

ANIMAL AGRICULTURE

Antibiotics are routinely used on animals, either to prevent disease or as growth promoters. Worldwide, significantly higher volumes of antibiotics are used in food animals than in human medicine. These antibiotic residues, can be passed on to humans through consumption of meat or dairy products. Antibiotics can also enter the environment at this point through animal excretion (with most of the active ingredient unmetabolised) and run-off from farms. Superbugs can be passed on directly from livestock to the humans who tend them.

INTERNATIONAL TRAVEL:

Antibiotic-resistant bacteria can be carried by travellers, who can then transport superbugs around the world.

PHARMACEUTICAL MANUFACTURING FACILITIES

Factories where antibiotics are produced are major point sources of antibiotic residues, notably in China and India, where most of the world's antibiotics are made. In an alarming number of cases, manufacturers simply dump untreated waste in the environment, or fail to treat it appropriately.

HOSPITALS

Hospitals are a key point source for AMR as they contain large numbers of people using a cocktail of different antibiotics. High levels of different antibiotics in excreted matter passes directly into rivers or through wastewater plants that are often unable to filter antibiotic residues.

TOWNS & HOUSES

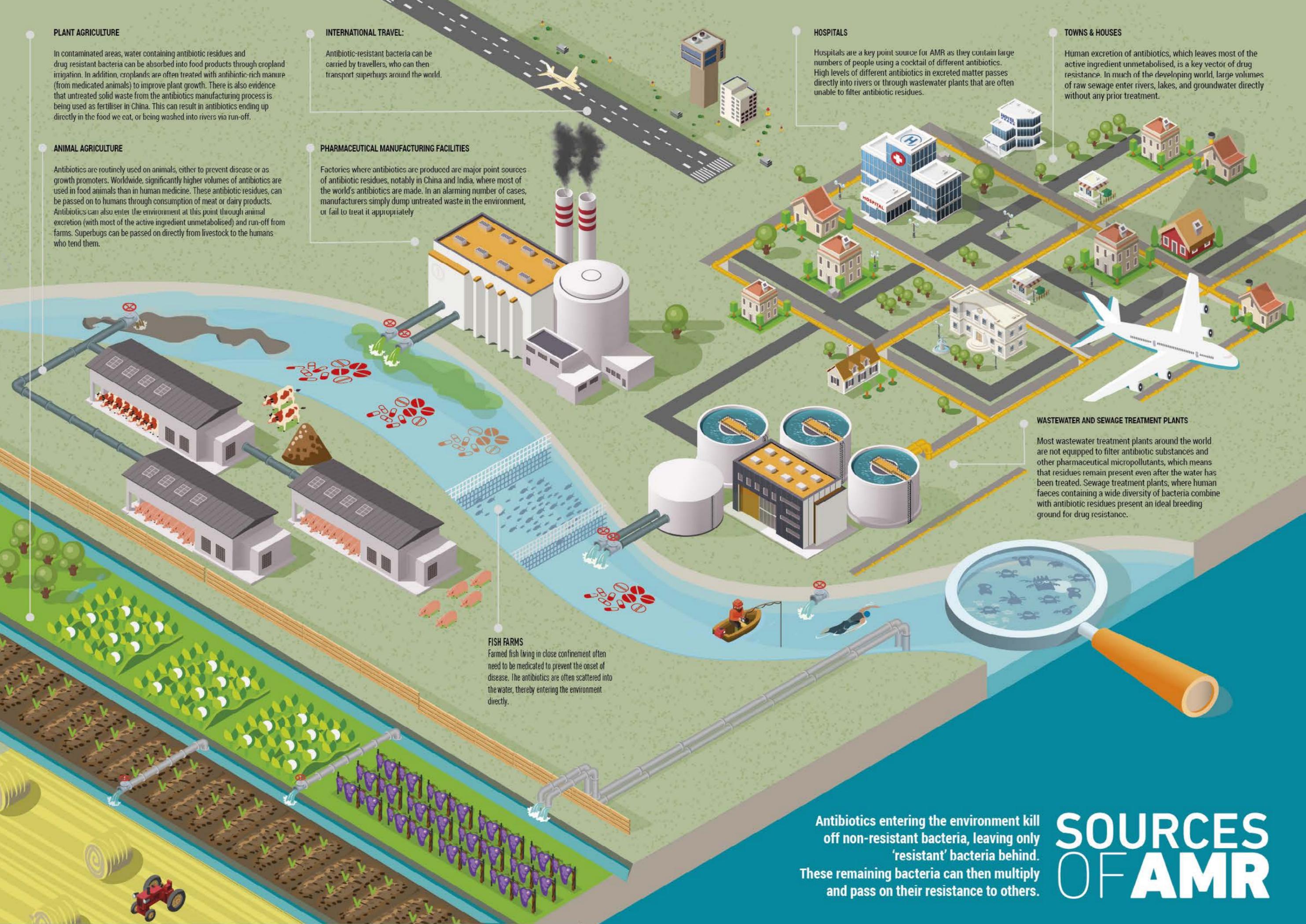
Human excretion of antibiotics, which leaves most of the active ingredient unmetabolised, is a key vector of drug resistance. In much of the developing world, large volumes of raw sewage enter rivers, lakes, and groundwater directly without any prior treatment.

WASTEWATER AND SEWAGE TREATMENT PLANTS

Most wastewater treatment plants around the world are not equipped to filter antibiotic substances and other pharmaceutical micropollutants, which means that residues remain present even after the water has been treated. Sewage treatment plants, where human faeces containing a wide diversity of bacteria combine with antibiotic residues present an ideal breeding ground for drug resistance.

FISH FARMS

Farmed fish living in close confinement often need to be medicated to prevent the onset of disease. The antibiotics are often scattered into the water, thereby entering the environment directly.



Antibiotics entering the environment kill off non-resistant bacteria, leaving only 'resistant' bacteria behind. These remaining bacteria can then multiply and pass on their resistance to others.

SOURCES OF AMR



Black water flows downstream of the Guddapatharam Industrial Area, near Kazipally, Hyderabad.

PART 2

Sampling

This section reports on the discovery of *E. coli* bacteria resistant to multiple antibiotics in water samples taken from selected sites in India by the investigative agency Ecostorm and tested under the supervision of Dr Mark Holmes from the University of Cambridge in summer 2016.

The purpose of the sampling was twofold. The first objective was to investigate for presence and levels of antimicrobial resistance (AMR) in water directly adjacent to factories manufacturing antibiotics in industrial areas surrounding Hyderabad, Visakhapatnam, Delhi and Chennai, where preliminary research had indicated that effluent might be emanating from their premises. The second objective was to build up a picture of the extent to which pollution from antibiotics manufacturing impacts overall levels of resistance in bacteria taken from local water bodies and at water treatment plants, including Asia's largest sewage treatment plant in the Hyderabad suburb of Amberpet.

1. Summary of results

With a growing body of scientific evidence on the presence of antibiotic waste and the development of drug resistance in the vicinity of factories in India (see box), the investigation described below set out to shed more light on the pharmaceutical pollution crisis which has been unfolding in numerous locations across India over several decades. Given that the Indian pharmaceutical industry is geographically dispersed and located in various clusters around the country, it is likely that the findings presented here are merely the tip of the iceberg when it comes to the existence of pharmaceutical pollution-related AMR in India.

E. coli bacteria cultivated from water samples taken at selected sites in India including factories manufacturing antibiotics, a sewage treatment plant receiving effluent from drug production facilities, and water bodies in the vicinity of industrial areas were tested for resistance to: Cefepime, Cefpodoxime, Ceftazidime, Cefotaxime (all cephalosporin antibiotics), Ertapenem (a carbapenem) and Ciprofloxacin (a fluoroquinolone), which are all commonly manufactured in India. Ertapenem and Ciprofloxacin were used as proxies for the detection of wider resistance to the antibiotic classes they belong to, respectively the carbapenems and fluoroquinolones.

In total, out of 34 sites tested, 16 were found to be harbouring bacteria resistant to antibiotics. Of the 18 sites where resistance was not detected, 12 samples contained no bacteria and could therefore not be tested for resistance in the first place. The absence of bacteria could be related to the presence of a substance toxic to the bacteria in the water. In addition to this, the investigation team also took control samples from water sources in each of the four regions visited.

Of the antibiotics manufacturing plants tested, three factories respectively belonging to **Aurobindo Pharma (Hyderabad), Orchid Chemicals (Chennai), and Asiatic Drugs and Pharmaceuticals (Delhi) were found to be resistance hotspots.**

At **four of the sites:** Aurobindo's Unit VII in Polepally, 80km southwest of Hyderabad; the Orchid Chemicals plant in Chennai; the Amberpet Sewage Treatment plant; and a tributary of the Musi River, **resistance to all 6 antibiotics, indicating resistance to three major classes of antibiotics, namely the cephalosporins, carbapenems and the fluoroquinolones (see box), was detected.**

At **eight of the sites, resistance to cephalosporins and fluoroquinolones** was detected. At a further **four of the sites, resistance to either cephalosporins or fluoroquinolones** was found, as described below.



ANTIBIOTICS TESTED:

Cefepime, Cefpodoxime, Ceftazidime and Cefotaxime are cephalosporin antibiotics. The cephalosporins are broad-spectrum antibiotics (i.e. effective for a broad range of infections) which are widely used for the treatment of septicaemia, pneumonia, meningitis, biliary-tract infections, peritonitis, and urinary-tract infections. They are also commonly used in surgical prophylaxis, i.e. to prevent infection following an operation.

Ertapenem is a carbapenem antibiotic. Carbapenems play a critical role in our antibiotic arsenal. Often used as “antibiotics of last resort”, they are broadly active antibacterials that are used for infections caused by difficult to treat or multidrug-resistant bacteria, such as ESBL-expressing *Klebsiella pneumoniae*. Multi-drug resistant *K. pneumoniae* has emerged as an important cause of hospital-acquired infections, especially among newborn babies.

Ciprofloxacin is a fluoroquinolone antibiotic. Also classified as “drugs of last resort”, fluoroquinolones have a broad-spectrum of activity and play an important role in treatment of serious bacterial infections, especially hospital-acquired infections and others in which resistance to older antibacterial classes is suspected. Common fluoroquinolone brand names are Cipro (**Ciprofloxacin**), Levaquin (**Levofloxacin**) and Avelox (**Moxifloxacin**). In 2010, Levaquin was the best-selling antibiotic in the United States²⁵. Frequently misprescribed to treat relatively minor ailments, fluoroquinolones have powerful and potentially disabling side-effects including retinal detachment and acute kidney failure.

2. The sampling sites – Resistance hotspots

To the authors’ knowledge, this report represents the first time levels of drug resistance in the vicinity of specific factories producing antibiotics for global markets have been tested and made public. Building on extensive desk research and intelligence gathered during a trip to Telangana and Andhra Pradesh in January 2016 for a report commissioned by the Swedish investment bank Nordea Asset Management in March 2016²⁶, it shows that the irresponsible and illegal manufacturing practices which have blighted the region for decades, and are contributing to the development of AMR, continue unabated. In addition to revisiting previously inspected sites, the investigation team travelled to several new locations, including factories in Chennai and Delhi, to provide an indication of how widespread the problem is. The discovery of drug resistance at the new locations suggests that pollution at antibiotics manufacturing sites is indeed a national scourge.

A SHORT HISTORY OF ANTIBIOTICS POLLUTION AND DRUG-RESISTANCE IN HYDERABAD



Ciprofloxacin has been the focus of a number of scientific studies about pharmaceutical pollution in Hyderabad, the centre of India’s bulk drug manufacturing industry, over the past decade. In 2007, a team of Swedish scientists, analysed pharmaceuticals in the effluent from a wastewater treatment plant serving about 90 pharmaceutical manufacturers in Patancheru, an industrial zone situated on the outskirts of the city. The pharmaceutical concentrations in some of the water samples they took at the Patancheru Common Effluent Treatment Plant (CETP) were higher than those found in the blood of patients taking medicine. The concentration of Ciprofloxacin, was approximately one million times greater than the levels that are regularly found in treated municipal sewage effluent²⁷ and toxic to a range of organisms. The estimated total release of Ciprofloxacin for 1 day was 44 kg, which is equivalent to Sweden’s entire consumption over 5 days, or, to take a different measure, sufficient to treat everyone in a city of 44,000 inhabitants. Follow-up studies showed that the pharmaceutical pollution had contaminated river sediment²⁸, soils²⁹, and surface, ground and drinking water³⁰ to unprecedented levels. In 2013, researchers also detected multi-drug resistance at the site³¹.

A follow-up study in 2014 on Kazipally Lake, which is located in the vicinity of Patancheru, and is affected by the dumping of waste from pharmaceutical production established that it harboured a wide range of resistance genes (81 identified gene types) against “essentially every major class of antibiotics”, as well as genes responsible for mobilisation of genetic material. Resistance genes were estimated to be 7,000 times more abundant than in a Swedish lake included for comparison, where only eight resistance genes were found³².

In 2016, researchers from the Indian Institute of Technology found “exceptionally high” concentrations of ciprofloxacin at the Amberpet Sewage Treatment Plant (STP), located in downtown Hyderabad, which receives effluent directly from the Patancheru CETP via an 18km-long pipeline, as well as in the Musi River, a major water course which runs through Hyderabad. Concentrations of antibiotics were highest at the inlet of the STP³³.

The Patancheru-Bollaram industrial cluster has been identified as being ‘critically polluted’ using India’s Central Pollution Control Board Comprehensive Environmental Pollution Index (CEPI)³⁴, and a Senior Advocate of the Indian Supreme Court recently described the CETP itself as “a major source of pollution”, noting that “if the Government of Telangana does not wake up to the stark reality of large-scale environmental degradation in Patancheru-Bollaram Industrial Estates, it could turn out to be a Bhopal tragedy [in] slow motion”³⁵.



Green pools of effluent found surrounding Aurobindo's Unit 7 in Polepally, Hyderabad. Water was witnessed running from a purpose-built drain hole in the wall.

Company Profile:

AUROBINDO PHARMA LTD



Based in Hyderabad, Aurobindo Pharma Ltd. is one of India's largest vertically integrated pharmaceutical companies and its 4th largest producer of generic drugs³⁶. Specialising in anti-infectives, it manufactures both active pharmaceutical ingredients (APIs) and finished dose products. Through its large network of subsidiaries, the company has a significant global presence, employing 15,000 people from over 30 countries³⁷, and exporting products to over 150 countries around the world. Its commercial focus is on export markets, with more than 87% of its revenues derived from international activities³⁸. Drug production is mainly located around Hyderabad (18 manufacturing facilities) but the company also has manufacturing capacity in other parts of the world (3 manufacturing facilities in the U.S., 1 in Brazil)³⁹.

Aurobindo is a rapidly growing company, with an increase in revenues of over 800% over the past decade⁴⁰ and target revenues of \$3 billion for 2017-18⁴¹. This success has been achieved in large part due to a series of international acquisitions, a diversion of its business focus away from APIs and towards finished dose products, and the creation of its own brand to manufacture, market and distribute 'store brand' over-the-counter (OTC) products⁴², including to companies such as CVS Health⁴³. Aurobindo's biggest market in financial year 2015-16 was the United States (55%), where it claims to be the No.7 prescription supplier⁴⁴, followed by Europe (28%)⁴⁵. The acquisition of Actavis' operations in seven EU member states in 2014⁴⁶ significantly increased the company's European market share⁴⁷. With their position also strengthened by the acquisition of the UK's Milpharm Pharma Ltd. in 2006, and the establishment of APL Swift Services in Malta, which it sees as a "gateway" to the European market⁴⁸, it now supplies EU markets directly with Aurobindo-made drugs under a number of different brands (see below).

Aurobindo Unit VII, Polepally, Mahaboobnagar District

Aurobindo Pharma's Unit VII is located 80km south-west of Hyderabad in Polepally Special Economic Zone (SEZ).

Since its construction in 2008 the plant has been mired in controversy, stemming first from the alleged "forcible acquisition" of land from farmers and widespread protests over the non-receipt of promised compensation⁴⁹. By October that year, complaints were already being voiced over the levels of pharmaceutical pollution emanating from the SEZ⁵⁰.

Unit VII is a very important facility for Aurobindo and, as of May 2016, had 76 Abbreviated New Drug Application (ANDA)⁵¹ approvals from the U.S. FDA, almost 30% of the company's total ANDA approvals⁵². The facility manufactures and processes antibiotic and anti-retroviral products before exporting them around the world.

Customs data and other official documents show that the plant does a roaring trade with the United States and Europe, with antibiotic substances representing a staple export. According to customs records, U.S. distribution giant McKesson received deliveries of the antibiotic Amoxicillin directly from Unit VII in 2015⁵³. Italian Medicines Agency paperwork from January 2016 likewise shows that Unit VII was involved in "primary and secondary manufacturing" of the fluoroquinolone antibiotic Ciprofloxacin supplied to the Italian market (Units I and III on the outskirts of Hyderabad were also listed). A number of European companies, including Aurobindo subsidiaries Milpharm Ltd. in the UK and APL Swift Services in Malta were named as occupying various functions relating to this production, including quality control and batch release⁵⁴.

According to U.S. customs data and medicines labels, other antibiotics manufactured at Unit VII include: Piperacillin, Penicillin, Moxifloxacin, Levofloxacin, Trimethoprim and Metronidazole. In January 2016, the U.S. FDA expressed concerns about manufacturing practices at Aurobindo's Unit VII in a "Form 483"⁵⁵.

Aurobindo subsidiaries in the EU and U.S.

EU:

- Milpharm Ltd. (UK)
- Arrow Génériques, formerly trading as Actavis France SAS (France)
- Puren Pharma GmbH, formerly trading as Actavis Deutschland GmbH & Co. (Germany)
- Aurobindo Pharma GmbH (Germany)
- APL Swift Services (Malta)
- Aurobindo Pharma (Malta)
- Aurobindo Benelux BV, Aurobindo-Pharmacin (Benelux countries)
- Agile Pharma BV (Netherlands)
- Aurex (Pharma (Netherlands)
- Aurobindo Pharma Italia S.r.l. (Italy)
- Aurovitas (Spain)

US:

- Aurobindo Pharma USA Inc. (also owns: Aurohealth LLC)
- Aurolife Pharma LLC
- AuroMedics Pharma LLC

***Non-exhaustive list based on information obtained from www.aurobindo.com and company websites.**



Wastewater pipe coming out of the wall of Orchid Pharma's antibiotic plant in Alathur, near Chennai. Orchid claims this site employs 'Zero Liquid Discharge' waste-water technology.

A. TOTAL RESISTANCE: Resistance to cephalosporins, carbapenems and fluoroquinolones was detected at the following locations

- **Aurobindo VII, at Polepally, 80km southwest of Hyderabad.** The plant is situated inside the Green Industrial Park, a fairly modern complex. The front is guarded by security personnel, but on touring the perimeter the investigation team observed apparent standing effluent in a pool halfway down the right side of the block and adjacent to the perimeter wall. At the rear of the block, there was a clearly visible and steady stream of apparent wastewater emerging from the perimeter wall above ground level through cracks, and forming into pools and puddles of water in the surrounding verge before trickling away down the road - the samples were taken from here.
- **Orchid Chemicals plant located in SIDCO industrial area at Alathur, south of Chennai.** Orchid appears to be the most significant and largest company based at this site. The investigation team encountered heavy security around the main plant area, with guards

and CCTV. There were also signs on walls prohibiting photography or use of cell phones around the plant. At the main plot, the investigation team were informed that the plant behind it, separated by a road, also belonged to Orchid. Wastewater was seen in a gully running adjacent to the second plant (i.e. just across the road from the first plant), emanating from an open discharge pipe coming from the site, next to which the samples were taken.

- **Musi River tributary at Edulabad on the outskirts of Hyderabad, close to Pedhagudam Village.** Effluent foam was clearly visible on the surface of the river where the water samples were taken. This river tributary and others directly feed all the surrounding rice paddy via pipes.
- **Amberpet Sewage Treatment Plant.** The Amberpet Sewage Treatment Plant (STP) is a major facility to the south of Hyderabad's Hussein Nagar Lake. Billed as "Asia's largest sewage treatment plant", it receives pharmaceutical effluent channelled through an 18km-long pipeline from the Patancheru Common Effluent Treatment Plant (CETP), which serves a large number of pharmaceutical manufacturing plants. Record levels of Ciprofloxacin were recorded at the Patancheru CETP in a 2007 study⁶³, and in 2013, researchers detected multi-drug resistance at the site⁶⁴. More recently, researchers found "exceptionally high" concentrations of Ciprofloxacin at the Amberpet STP and in the Musi River in 2016. Concentrations of antibiotics were highest at the inlet of the STP⁶⁵ (see box on for details).

Company Profile:

ORCHID CHEMICALS



Orchid Pharmaceuticals is an Indian pharmaceutical company based near Chennai, in Tamil Nadu Province. The company produces a wide variety of cephalosporins, a family of broad-spectrum antibiotics, for both domestic and veterinary use, as well as a range of non-antibiotic products⁵⁶. The company has

global reach, and lays claim to a presence through joint ventures and partnerships in over 70 countries⁵⁷. Facilities include one API manufacturing site, three formulations manufacturing sites, and three 'research campuses', all located in India.

Orchid prides itself on its record on environmental protection, which it states is the company's "prime concern"⁵⁸. It claims that its API manufacturing facility in Alathur, has the first "zero discharge environment friendly effluent treatment plant in India"⁵⁹. However, the investigation carried out for this report found a discharge pipe coming from a perimeter wall at the plant, and water samples taken from a ditch adjacent to the plant's perimeter wall subsequently tested positive antibiotic-resistant bacteria.

Orchid's Alathur plant has been approved many times by global regulatory agencies, although it should be noted that at present, such approvals do not take any environmental criteria into account (see Part 3). The plant was last inspected by the U.S. FDA and approved for export in April 2016.⁶⁰ Shares rose over 13% on this approval.⁶¹

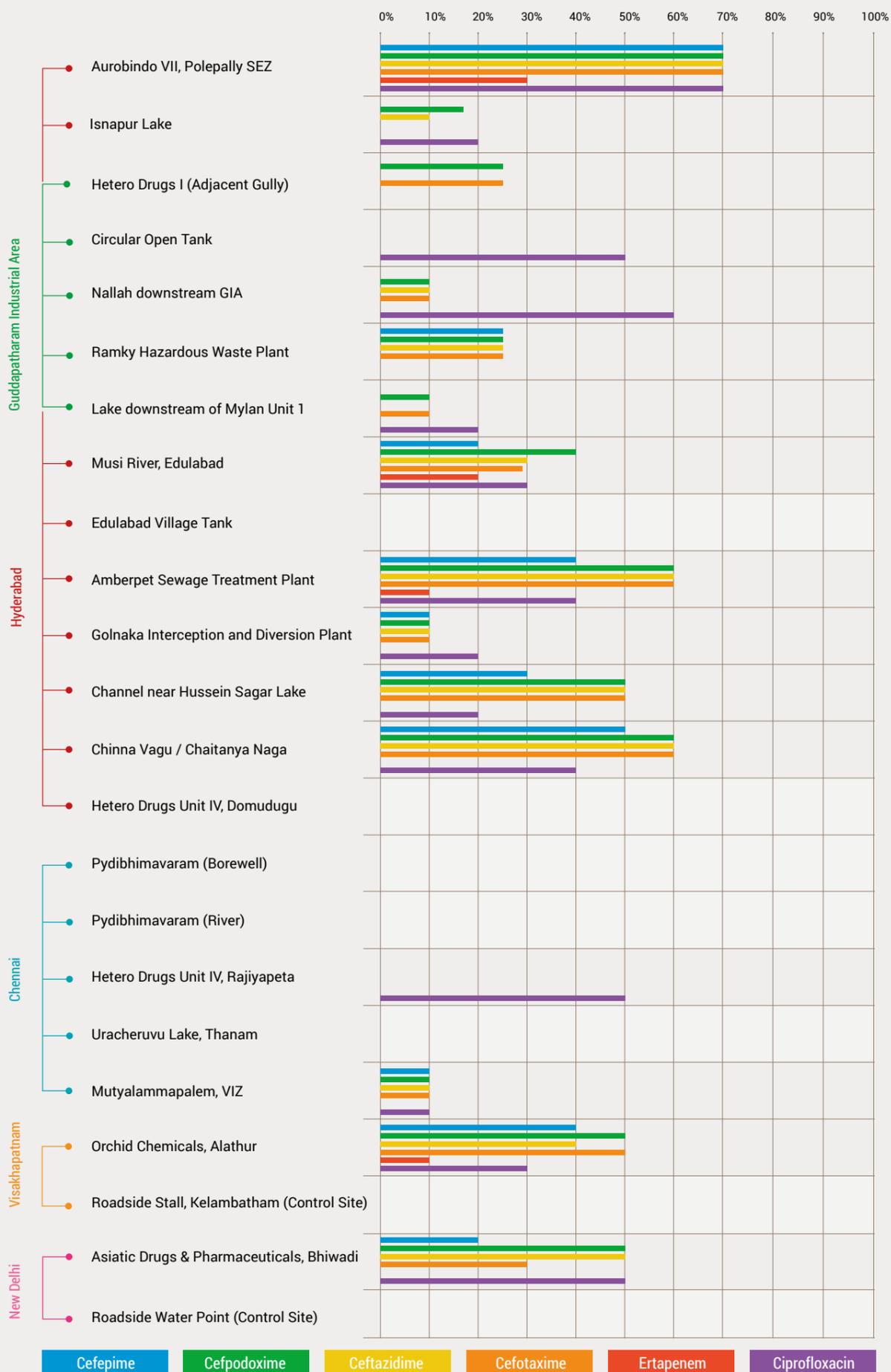
In addition to its UK-based subsidiary, Orchid Europe Ltd., supply chain research has identified export links between Orchid Chemicals and EU-based pharmaceutical distributors, explored at greater length in Part 3 of this report. Orchid Chemicals also has two U.S.-based subsidiaries, Organus Pharma and Orchid Pharma US and owns stakes in Bexel Pharmaceutical Inc. and Diakron Pharmaceuticals, Inc.⁶²



Rice paddies irrigated by water from the Musi River

RESULTS OF ANTIBIOTIC TESTING

% OF E. COLI COLONIES RESISTANT TO ANTIBIOTICS



Company Profile:

ASIATIC DRUGS AND PHARMACEUTICALS



Little is known about Asiatic Drugs & Pharmaceuticals Ltd. It was founded in 1998 and has one manufacturing facility in the RIICO Industrial Area, Bhiwadi, to the south-west of New Delhi. The company specialises in making cephalosporin antibiotics, including Cefpodoxime, Cefuroxime, and Cephalexin, and penicillin antibiotics such as Amoxicillin, Ampicillin, Flucloxacillin. Its domestic customers include a wide range of Indian small-and-medium sized companies (SMEs), several of which are listed API exporters to the EU, as well as DSM Anti-Infectives India Ltd, a subsidiary of Dutch group Royal DSM⁶⁶.

Small, specialised API companies such as Asiatic Drugs and Pharmaceuticals are very common across India, supplying larger companies which create finished-dose products or export directly to overseas markets⁶⁷. This makes identifying all actors in the supply chain for a given medicinal product a near-impossible task, even for regulators.

B. EXTREME RESISTANCE: Resistance to fluoroquinolones and cephalosporins

Resistance to cephalosporins and fluoroquinolones was detected in water samples taken from the following sites:

- **Asiatic Drugs and Pharmaceuticals, Delhi.** Samples were taken from dirty-looking and malodorous wastewater in a gully at the front corner of the plant, fed by pipes coming from inside the site.
- **Gaddapotharam industrial area, Hyderabad: large lake in the vicinity of Mylan's Unit I and Aurobindo's Unit XIII.** Mylan claims to be a leader in India in "zero liquid discharge (ZLD)" and states that all of its manufacturing plants in Hyderabad are ZLD plants⁶⁸. However, the investigation team was informed that the Mylan I plant discharges into this lake, which is downstream of the factory. The team heard claims that Aurobindo's Unit XIII, which is upstream of the lake, was discharging into the nearby circular tank and down into the open nallah⁶⁹ which runs downstream of it (see next point). According to data from India's Central Drugs Standard Control Organisation (CDSCO), Mylan's Unit I produces a range of pharmaceuticals, including the antibiotics Moxifloxacin and Gatifloxacin (both fluoroquinolones), and Clindamycin, which is used primarily to treat anaerobic infections such as bone and joint infections.
- **Open nallah which runs downstream from the Gaddapotharam industrial area towards the Kazipally valley and tank systems, Hyderabad.** The water was gushing fairly profusely and fast down the nallah from the industrial area, and was black in colour. The investigation team was informed that waste discharges from Aurobindo's Unit XIII are flowing into this nallah.



- **Isnapur Lake adjacent to the Pashamylaram industrial area, Hyderabad.** Water samples were taken from a flowing gully which carries wastewater from the industrial area into the lake. The team visited the Aurobindo V plant which is situated inside the industrial area but very near to the lake, however no wastewater was visible around the perimeter of the plant, only pipes.

Dirty water leaving the Golnaka Interception and Diversion Plant in Hyderabad, heading towards the Musi River

Woman sorting fish on the beach near Tikkavanipalem village, Andhra Pradesh



Livestock drink water collected in pools downstream of Hetero Drugs Unit 1, near Domudugu Village, Hyderabad.



Pipes protruding from exterior wall of Ramky Hazardous Waste Water Plant, Hyderabad.

- Golnaka I&D (Interception and Diversion).** The I&D plant channels effluent into the Amberpet Sewage Treatment Plant from various sources. This plant is situated at the mouth of a wide nallah which leads out from the bottom of Hyderabad's Hussein Sagar lake, and is discharging large volumes of city waste directly into the river beyond the plant. Water samples were obtained inside the plant. Staff there said 10% of the input (coming down the open nallah from Hussein Sagar Lake and joined from elsewhere en route) goes towards the Amberpet STP, and 90% goes untreated into a 'surplus' nallah which flows towards the Musi River and eventually joins it. The samples were taken from this surplus nallah.

- Channel near Hussein Sagar lake, upstream from the Golnaka I&D plant.** The investigation team followed the route of the incoming nallah, and sampled at a spot close to Hussein Sagar Lake. Sampling was taken from a channel flowing with wastewater before it meets with the Hussein Sagar flow.

- Chinna Vagu/Chaitanya Nagar Colony (village).** There was a wide and heavily polluted open nallah flowing through here, with effluent foam on the surface. To one side of the nallah, a pond had formed, in which two farmers were working waist-deep and catfish were swimming.

- Seawater at coast near Visakhapatnam, at end point of Jawaharlal Nehru Pharma City (JNPC) wastewater pipeline, Tikkavanipalem village.** The JNPC is the main hub of pharmaceutical activity in the Visakhapatnam area and houses a 'Special Export Zone' (SEZ) which plays host to numerous foreign pharmaceutical companies, including U.S. giant Mylan, Pfizer subsidiary Hospira, Japan's Eisai, Germany's Pharma Zell and India's own SMS Pharmaceuti-

cals⁷⁰. Other clients apparently operating outside the SEZ include Indian companies Aurobindo, Hetero and Lupin Laboratories⁷¹. The JNPC pipeline is buried in the sand and eventually emerges from seabed several hundred metres out. The tide was coming in, and sampling was taken at the water's edge approximately in line with the pipecourse, which was apparent from concrete blocks laid on the sand to prevent the plastic pipe from surfacing over time.

C. HIGH RESISTANCE: Resistance to cephalosporins or fluoroquinolones

i. Resistance to cephalosporins:

- Gully directly adjacent to Hetero Unit I, Gaddapotharam industrial area.** Water samples were taken from the gully emerging from under the plant gates.
- Ramky Hazardous Waste plant, Gaddapotharam industrial area.** Samples were taken from standing pools directly adjacent to the rear perimeter, just below a CCTV camera and watchtower. The water was clearly emerging from inside the plant.

ii. Resistance to fluoroquinolones:

- Circular open tank, Gaddapotharam industrial area.** The water samples were taken from the central part of the tank, where the water is standing rather than running through and out. The water was black and appeared to be full of chemical residues and particulate.
- Hetero IV plant at Rajiyapeta, south of Visakhapatnam.** Sampling was taken at the corner of the large village tank/reservoir directly adjacent to the plant perimeter. The day prior to the investigation team's visit, there had been an accident at the plant leading to one fatality and leaving two people critically injured after an explosion in a waste drum emanating from the drug production unit, followed by mass demonstrations by workers over safety lapses and inadequacies on the part of the owners. The team heard from an informant that Hetero settled out of court with the family of the deceased man within hours via brokering by the village heads, who are alleged to be in the pay of the company. This would prevent a court case and any admission of negligence or further compensation on the part of Hetero - a common pattern. The informant also claimed that the plant pays 5,000 INR per month to the police 'unofficially' for protection. When the team drove past the main entrance of the factory, riot police vans were observed parked outside.

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Rampant pollution in Hyderabad industrial areas

By Prashant Nandy Reddy | THE HANS INDIA | 04 Jun 2015, 11:38 PM IST

On the UN-declared World Environment Day on June 5, observed the world over, it has become a ritual to think of the most contaminated sites, from the point of view of environmental degradation. One such patch on the face of the Earth is located on the outskirts of the Hyderabad city at Patancheru – Bollaram Industrial Estates, where more than 200 pharmaceutical manufacturing units are located, contributing 30% of India's bulk drug exports and likewise earning the much sought after foreign exchange for the State exchequer.

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PHARMA MANUFACTURING MARKETING PHARMA ASIA ANIMAL HEALTH DRUG DELIVERY VACCINE

Manufacturing

FDA finds China manufacturing plant full of holes, chipped paint and insects

by Eric Palmer | Aug 31, 2016 3:10pm

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Pollution puts pharmaceutical supply chains under the spotlight

Rivers of shame spur manager to take action

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India relies on China for 90 per cent of drug raw materials

By Soma Chel, ET Bureau | Updated: Oct 29, 2014, 03:43 AM IST

NEW DELHI: Imagine a situation where an Indian soldier's medical kit is running out of essential drugs on a battle front. This may sound like a figment of imagination, but given India's acute dependence on China for key ingredients (active pharmaceutical ingredients) for several essential drugs including several antibiotics, the prospect of such a scenario isn't that remote. India depends heavily on imports — over 90% — from China for many key raw materials (mostly intermediates and some active pharmaceutical ingredients) that go into the making of at least 15-odd essential drugs, reckons a Boston Consulting Group (BCG) and Confederation of Indian Industry (CII) report reviewed by ET.

India's acute dependence for key raw materials which are used to make at least 15 essential drugs can affect pharma industry if a situation arises where China stops their supply.

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Year	Approvals
2010	25
2011	27
2012	37
2013	56
2014	118
2015	111

PART 3

The Supply Chain

This report has highlighted how substandard manufacturing and waste treatment methods at Indian antibiotics production plants pose a danger to human health and the environment by creating drug-resistant bacteria. However, the problem is not confined to one country. Indeed, over 90 per cent of Indian drugs, including antibiotics, are manufactured using raw materials and APIs made in China²², frequently in conditions which are also believed to be fuelling the spread of drug resistance and blighting the lives of people living in the vicinity of plants.

The following section will provide background on China's role in the antibiotics supply chain, identifying on the basis of recent inspection reports a number of companies which have violated Good Manufacturing Practices (GMP), and exploring their ties with pharmaceutical companies in the United States and Europe (although GMP do not include environmental criteria, their infringement offers a good indicator of manufacturing problems and supply chain lapses). It will then offer a detailed – albeit partial – overview of the global antibiotics supply chain, covering China, India, the U.S., and EU, obtained following analysis of official databases, customs records, company information, inspection agency reports and on-the-ground investigations in China in December 2015 and June 2016 which found evidence of the persistence of pollution problems in several areas supplying drugs to global markets. Complemented with additional information on pollution in the vicinity of Chinese factories, the overall picture of antibiotics manufacturing which emerges is alarming.

1. Bad Manufacturing Practices: China's role in the antibiotics supply chain

Because pharmaceutical supply chains are so complex and opaque, mapping the journey of a pharmaceutical product from factory to pharmacy shelf is a challenging task. Measuring a drug's environmental impact in particular is near impossible: U.S. and EU regulations in the shape of the GMP framework focus on drug safety but do not currently oblige companies to implement environmental safeguards during the drug manufacturing process. These – together with labour standards – depend exclusively on the host country and company which produced the drugs. Facilities in India and China which export to Western markets are hence regularly inspected for GMP compliance, but these inspections cannot sanction a factory for polluting practices, lack of waste water treatment or any other environmental problems. Even where environmental regulations are in place, the monitoring and enforcement of these rests exclusively with local authorities and is often found lacking. In the case of antibiotics production, pollution should be taken especially seriously as it has consequences which go far beyond national borders, in the form of AMR.

Although GMP inspections can only offer a partial snapshot of conditions at pharmaceutical plants, U.S. FDA and European medical agency reports frequently highlight serious manufacturing deficiencies at Chinese plants known to be supplying antibiotic ingredients to Indian, U.S., and European companies, which in itself presents major grounds for concern about the drugs we import.

China's exports of pharmaceutical products and health supplements worldwide jumped 3 percent to \$56 billion in 2015. Nearly 5,000 drug factories supply its domestic market, while more than 500 facilities are registered to sell to the United

States⁷³. Official statistics show that EU imports of pharmaceuticals from China stood at \$2.8 billion in 2015⁷⁴, but this figure does not account for Indian pharmaceutical imports made with Chinese raw materials and APIs. China is currently the world's largest exporter of APIs⁷⁵, supplying over 50% of the global market⁷⁶ and is the number one producer of penicillin salts worldwide⁷⁷. Over 80% of Chinese-made penicillin salts are exported to India⁷⁸, where they are processed into end products and exported onwards to other markets around the world. In recent years, Chinese companies have also sought to carve out a bigger share of the market for finished pills around the world⁷⁹.

With China playing such a pivotal role in global pharmaceutical supply chains, industry watchers keep a close eye on events within the country's drug manufacturing sector. In a January 2016 analysis, the trade publication Pharma Compass identified the threat of antibiotic resistance emanating from China, coupled with Good Manufacturing Practice (GMP) compliance concerns at its manufacturing sites as the "two main issues threatening to disrupt the supply chain from China."⁸⁰

Chinese manufacturers have repeatedly hit the headlines as a result of infringing GMP rules or owing to their dismal environmental performance. In June 2015, an investigation released by the campaigning organisation SumOfUs lifted the lid on a series of serious pollution incidents at antibiotics manufacturing sites in China. The report "Bad Medicine: How the pharmaceutical industry is contributing to the global rise of antibiotic-resistant superbugs"⁸¹ showed how major pharmaceutical companies including Pfizer, Teva and McKesson had sourced antibiotics from some of these sites, including:

- United Laboratories – TUL (Bayannur, Inner Mongolia and Chengdu, Sichuan Province)
- Shandong Lukang (Jining, Shandong Province)
- North China Pharmaceutical Company – NCPC (Shijiazhuang, Hebei Province)
- CSPC Pharmaceutical Group (Shijiazhuang, Hebei Province)
- Sinopharm WeiQida (Datong, Shanxi Province)
- Harbin Pharmaceutical Group (Harbin, Heilongjiang Province)
- Tonglian Group (Hulun Buir, Inner Mongolia)
- Inner Mongolia Changsheng Pharmaceutical Co. Ltd. – formerly CSPC Pharmaceutical Group's Shiyao Zhongrun site (Hohhot, Inner Mongolia)

In 2015 alone, around 80 Chinese production sites were issued with a US FDA 'Form 483', which indicates that a company has committed manufacturing violations⁸². These sites include factories supplying multinational pharmaceutical companies, and in some cases, joint ventures with U.S. and European companies.

For example, in late 2015, the Zhejiang Hisun Pharmaceutical Co. plant in Taizhou, Zhejiang Province, which supplies companies including Hospira (now owned by Pfizer), and Merck & Co.,⁸³ was hit with a U.S. import ban on its products, including antibiotics, following an FDA inspection which highlighted various manufacturing deficiencies⁸⁴. Zhejiang-Hisun is part of a \$300 million joint venture with Pfizer (Hisun-Pfizer Pharmaceuticals Co., Ltd.), launched in September 2012 for the development, manufacture, and commercialization of a broad portfolio of products including pharmaceuticals to treat infectious disease⁸⁵.

In January 2016, a few months after the Zhejiang-Hisun ban, the US FDA banned U.S. imports of all antibiotics and drugs for human or animal use manufactured at the nearby Zhejiang Hisoar plant in Taizhou⁸⁶, again citing failure to comply with Good Manufacturing Practices⁸⁷. Zhejiang Hisoar, which built its reputation on the production of antibiotics such as Clindamycin⁸⁸, claims to supply drugs to Pfizer, BASF, Sanofi and Novartis⁸⁹. In fact, as reported by Bloomberg, a 2012 stock exchange filing shows that Hisoar has a 20-year agreement to supply antibiotic products to Pfizer Asia Manufacturing Pte Ltd., a subsidiary of the New York-based drugmaker⁹⁰. In addition to this, company documents show that in 2008, Zhejiang Hisoar entered into a "strategic production alliance" with German pharma giant Boehringer Ingelheim: in return for Boehringer's expertise and technical support, it was agreed that Zhejiang Hisoar would invest in new production facilities specifically for Boehringer Ingelheim at its new site in Chuannan, Zhejiang Province⁹¹.

EU inspectors have also cracked down on violations at Chinese pharmaceutical production sites. In 2015, The United Laboratories' (TUL) plant in Zhuhai, Guangdong province, which claims to be the world's largest manufacturer of the antibiotic Amoxicillin, received a statement of non-compliance from Romanian inspectors, who logged numerous problems, resulting in the withdrawal by the European Medicines Agency of Zhuhai United Laboratories' certificate for the sale of Amoxicillin sodium sterile, potassium clavulanate sterile and Amoxicillin sodium and potassium clavulanate sterile mix on the EU market⁹². A restricted certificate was issued for the use of these products in "critical medicinal substances" in Romania, France and the United Kingdom⁹³.

TUL is one of China's biggest antibiotics producers. Incorporated in the Cayman Islands, it has at least six production hubs dotted around China, including its plant in Zhuhai, which has seven production lines manufacturing thousands of tonnes of antibiotics every year. It also has plants in Inner Mongolia and Chengdu, Sichuan Province, which both featured in the SumOfUs "Bad Medicine" report. TUL's factory in Inner Mongolia has repeatedly been spotlighted in the media and pursued by the local authorities for improper waste management, including the dumping of waste water into nearby Lake Wuliangshuai. In 2008, the factory was ordered to suspend operations and install proper waste treatment after reports that the factory had secretly buried its waste in a 50-hectare pit. Effluent was also being discharged through



Effluent floating on the surface of a river downstream of Yui Market and Shenyuan Pharmaceuticals companies, Zhuhai.



Sewage coming from a house in Zhuhai into an open sewer.



Two sewage outfalls (one large, one small) coming from the walls of the Zhuhai United Laboratories, mixing effluent directly into the Nanpai River.



The polluted confluence of the Nanpai and Beipai rivers, under the provincial highway S3211. The building reflected in the water is the Zhuhai United Laboratories

irrigation ditches linking to the Yellow River⁹⁴.

According to TUL's Annual Report 2015, the company received "incentive subsidies" of HK\$29,986,000 to "encourage the operations of certain PRC [People's Republic of China] subsidiaries for the development of environmental[ly] friendly manufacturing, pollution prevention, development on export sales and advanced technology"⁹⁵ and in October 2015, Zhuhai United Laboratories was awarded the honorary title of "Clean Production Enterprise" of Guangdong Province. However, a site visit to Zhuhai United Laboratories in 2016 showed that the area surrounding the factory is far from clean.

Our investigators observed a "filthy scene with black, smelly and greasy water" in the area surrounding the plant. At the confluence of the Nanpai and Beipai rivers, which is close to where the factory stands, the surface of the water was covered with a layer of black sludge. The team observed a steaming sewage outlet discharging wastewater flowing with white foam, and could smell the "awful intense odour" from a distance. There are outlets placed every 10 metres for about 400

to 500 metres along this section of the river. On the riverbank opposite the northeastern corner of The United Laboratories plant, they saw white foam on the surface of the river, noting the water's "indescribable" odour.

The Zhuhai United Laboratories plant is located in the Sanzao Science and Technology Industrial Zone, one of the biggest pharmaceutical manufacturing hubs in Guangdong Province. Local residents in Sanzao complain that the water quality remains filthy and smelly despite several attempts to regulate pollution in the area adjacent to the Beipei River. v

According to the Sanzao municipal authorities, some plants are still discharging sewage into the river in secret. They and the local Environmental Protection Department have vowed to introduce stronger management, inspection, and enforcement to put a stop to the illegal sewage discharges. According to our sources, there is only one wastewater treatment plant in the area, which does not have the capacity to process the large volumes of effluent from all the plants in its catchment area and therefore serves "practically no function".

Case Study



A fertile environment for superbugs? Investigating claims that untreated manufacturing waste from antibiotics factories in China is being recycled into fertiliser

The antibiotics fermentation process produces large quantities of residues. Pharmaceutical residues are classified as hazardous waste in China's National Hazardous Wastes Catalogue⁹⁶, which means that they should be incinerated or buried so as to make sure the waste is strictly "sanitised, inactivated, destructed, and hazard-free". Manufacturers rarely opt for incineration owing to the cost involved, instead choosing to repurpose the residues for use elsewhere.

Prior to 2002, Chinese pharmaceutical manufacturers would commonly turn antibiotics manufacturing residues into animal feed additives, which were then sold on the open market, where there was high demand owing to their protein and antibiotic contents. In February 2002, this use was officially banned by the Chinese Government⁹⁷. Since then, transforming antibiotic residues into fertiliser is reported to have become pharmaceutical manufacturers' preferred solution for disposing of solid waste. While experts see this as highly problematic from an environmental and human health perspective, the lack of specific laws or regulations covering fertiliser provides companies with a legal loophole which they are only too keen to exploit.

Shandong Lukang Pharmaceutical Co.

Shandong Lukang Pharmaceutical Co. is the self-styled "leading manufacturer of antibiotic products in China", manufacturing a wide variety of antibiotic APIs and intermediates⁹⁸. It has also come under fire for discharging antibiotic effluent into the environment: in 2014, China's state broadcaster CCTV revealed that wastewater from one of the company's production units contained over 50,000 nanograms of antibiotics per litre, about 10,000 times higher than the concentrations present in clean water⁹⁹. Desk research, site visits to a Lukang factory and interviews with local people as part of an investigation for this report in summer 2016 suggested that the company has also been selling solid waste from the pharmaceutical manufacturing process for use as fertiliser for a number of years.

This appears to be borne out by official documents: a local Environmental Pollution Board Environ-

mental Impact Assessment relating to Lukang's veterinary antibiotic pollution of 12,000 tonnes per year shows that Lukang has signed a Hazardous Waste Disposal Entrusting Contract with Jining Lite Biotechnology Co. Ltd. for the disposal of fermentation residues¹⁰⁰. "Lite" is a company which makes fertilisers and feed¹⁰¹.

The marketing materials of another fertiliser manufacturer, Shandong Jining Jishan Biotech Co. Ltd., claim that "our product is developed by specialists from the Soil and Fertilizer Institute of Shandong Academy of Agricultural Science... main ingredients include soy bean meal, pharmaceutical residues from Lukang Pharmaceutical ... specially made...Green, eco-friendly, disease resisting, no-till farming organic fertilizer."

At a fertiliser market in Shouguang City, Shandong Province, a large vegetable production hub, our investigators were shown bags of fertiliser labeled "Yuanhong Pai Soy Bean Meal Organic Fertilizer". On the back of the bags, they read "Ingredients include raw materials from Lukang [Corporation] (high quality soy bean meal, animal protein) and humus, features and functions include resisting and reducing plant diseases and pests".

The owner of the shop told them that there were 40 stores in the area selling the same fertiliser. Every day, millions of tonnes of vegetables are delivered from Shouguang to locations all over China as well as to overseas markets.



Online product listing for fertiliser containing amongst, others things 'pharmaceutical residues from Lukang Pharmaceutical'



Dead vegetation in the riverbed near the Zhuhai United Laboratories plant in Guangdong, China

National Agency for Medicines and Medical Devices

Report No: NCF/011/RO

STATEMENT OF NON-COMPLIANCE WITH GMP

Exchange of information between National Competent Authorities (NCAs) of the EEA following the discovery of serious GMP non-compliance at a manufacturer¹

Part 1

Issued following an inspection in accordance with :
 Art. 111(7) of Directive 2001/83/EC as amended
 The competent authority of Romania confirms the following:
 The manufacturer: **ZHUHAI UNITED LABORATORIES CO., LTD**
 Site address: *Sanzao Science & Technology Park, National Hi-Tech Zone, Zhuhai, Guangdong, 519040, China*

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on **2015-04-02**, it is considered that **it does not comply with the Good Manufacturing Practice** requirements referred to in

- The principles of GMP for active substances referred to in Article 47 of Directive 2001/83/EC.

¹ The statement of non-compliance referred to in paragraph 111(7) of Directive 2001/83/EC and 80(7) of Directive 2001/82/EC, as amended, shall also be required for imports coming from third countries into a Member State.

2. The supply chain from China to India and on to global markets

Global drug supply chains are cloaked in secrecy, which makes it impossible to provide anything more than a fragment- ed overview of the origin and end destination of specific pharmaceuticals. The information displayed on the following pages was obtained from desk research and careful examination of data from the following publicly available sources:

EudraGMDP Database:¹⁰²

The EudraGMDP database is maintained and operated by the European Medicines Agency (EMA). In addition to EU GMP inspection reports, it contains the registration documents for manufacturers, distributors and importers of APIs into the EU. It is open to all EEA member states (EU plus Iceland, Liechtenstein and Norway) and allows public access to the information in the database “that is not of a commercially or personally confidential nature”¹⁰³. EEA member states enter data into the EudraGMDP database as it becomes available. While a valuable source of information on which ‘third country’ manufacturing sites are supplying the European market, it is incomplete as not all competent authorities in Europe have established systems for timely inclusion of registration data. In particular, there are very few entries for imports to France and Germany¹⁰⁴.

U.S. Customs data available on Port Examiner:¹⁰⁵

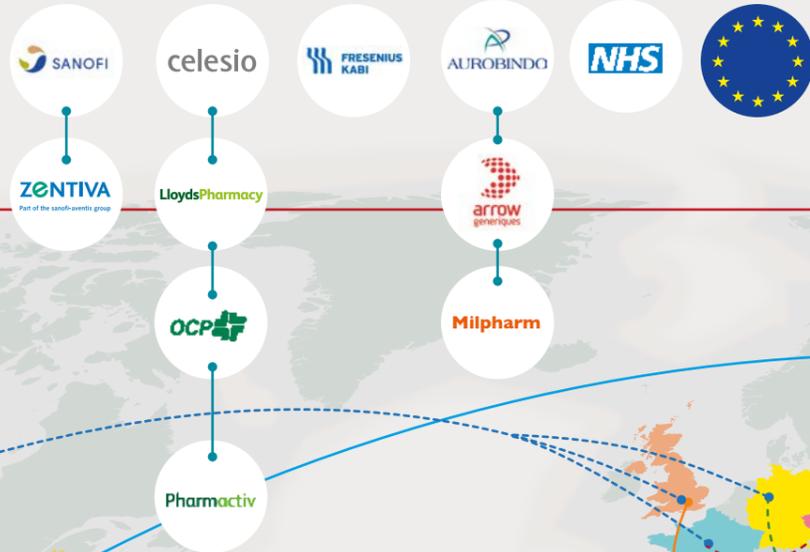
This website is a compilation of U.S. customs import records providing information on specific shipments to U.S. sea- ports. This comprises the bill of lading and customs declaration, which contain details on the identity and address of the company shipping the goods (down to the production site in the case of pharmaceuticals), the company receiving the goods in the U.S., as well as a description of the cargo’s contents (APIs are described by specific API name) and weight.

Indian Central Drugs Standards Control Organisation (CDSCO):

Indian Government site hosted by the country’s Ministry of Health. Users can access drug import and export databases which provide data on pharmaceutical substances (including antibiotics) being imported into India¹⁰⁶ as well as fre- quently updated information on Indian companies authorised to export to the EU¹⁰⁷. Listed are names and addresses of companies (including manufacturing unit numbers), the specific API products authorised for export, as well as the export licence start and end dates.

EU market players with links to polluting pharma companies in India and China.

French drugs giant **Sanofi** has links to dirty production via its Czech subsidiary **Zentiva**, which sources the antibiotic Ciprofloxacin from **Neuland Pharmaceuticals** - an Indian pharma company that has been implicated in unlawful manufacturing discharges.



Polluting Chinese companies have links to the EU and U.S. markets, either directly or through preliminary export to India. Italy's **Fresenius Kabi Anti-Infectives** imports the antibiotics Ampicillin and Benzylpenicillin from **CSPC Zhongnuo**, a Chinese pharma company subject to a U.S. import ban.

Polluting or non-GMP-compliant Chinese companies with EU/US market links



Supply chain research found **NHS** Trusts to be sourcing **Aurobindo** products directly, or through other brands under its ownership, including **Milpharm**, **Arrow Generics**, and Aurobindo's own brand.

Pfizer has long-standing ties with polluting pharma companies in India and China. In addition to sourcing antibiotic products from **Aurobindo** in India, it has joint venture agreements with **Zhejiang-Hisun** and **Zhejiang Hisoar** in China - two companies hit by recent U.S. import bans on their products, including antibiotics. Its subsidiary **Hospira** has been marred by a series of GMP scandals, most recently resulting in an EU import suspension on 6 antibiotic products in August 2016.

Aurobindo Unit VII in Polepally, near Hyderabad, directly supply antibiotics to **McKesson**, a San Francisco-based pharma distribution giant which delivers one-third of all medications used daily in North America. These are sold under McKesson's **NorthStar Rx** brand across the United States. **McKesson** also has strong links to U.S. pharmacy giant **CVS Health**, its single largest customer, to which it sold \$40 billion worth of products in the year ending March 2016. Following its acquisition of the German pharmacy conglomerate **Celesio** in 2014, McKesson is also a major player in the EU, and owns the **Lloyds Pharmacy** chain (the second biggest pharmacy in the UK), and leading French pharmacies, **OCP** and **Pharmactiv**.

India's **Parabolic Drugs** - a company that itself has a string of manufacturing violations to its name - imports the antibiotic Ceftriaxone from **CSPC Zhongnuo** before exporting on to **Midas Pharma** in Greece.

Polluting Indian companies producing antibiotics for the European and US markets.



DRUG RESISTANT BACTERIA FOUND

GLOBAL ANTIBIOTICS SUPPLY CHAIN

Case Study Aurobindo Pharma



Based in Hyderabad, India, Aurobindo Pharma has both direct and indirect links to China and Western export markets, and offers a representative case study of a pharmaceutical producer present in key geographical locations and at each stage of the global antibiotics manufacturing chain. Building on the information presented in Part 2 of this report, the following section will tease out some of these connections.

Analysis of recent CDSCO import licenses reveals that that Aurobindo's Units V and VI in Patancheru, on the outskirts of Hyderabad, have a licence to import Ceftriaxone sodium, a cephalosporin antibiotic, from Sinopharm Weiqida Pharmaceutical company's site in Datong, Shanxi Province¹⁰⁸. In recent years, Sinopharm Weiqida in Datong has received repeated criticism from the local environmental pollution board (EPB). In 2013, it came under fire for discharging 30,000 tonnes of black sludge, the majority of which was pharmaceutical wastewater, into the Sanggan River to the south of Datong. A waste treatment plant used by several Sinopharm subsidiaries was also found to be discharging effluent into the Yuhe River¹⁰⁹. According to its 2016 Annual Report Aurobindo has a 10% stake in Sino-Pharma Group Datong Weiqida in addition to its 100% ownership of the Chinese company All Pharma (Shanghai) Trading Company Ltd.¹¹⁰ which is "responsible for all business in Mainland China"¹¹¹.

The import licenses also show that Aurobindo has sourced Ceftriaxone from the Zhuhai United Laboratories plant in Guangdong, another polluted site described in detail above¹¹².

In terms of export markets, Aurobindo has a sizeable market presence in the U.S., both through its own brands and those of its customers. Customs data shows multiple exports to the U.S. from Aurobindo's plants in Hyderabad. For example, in July 2016, a consignment of over 9 tonnes of the antibiotic Amoxicillin clavulanate potassium from Aurobindo's Unit VII plant in Polepally, a site identified in the previous section as harbouring drug-resistant bacteria, arrived at Aurobindo's U.S. subsidiary Aurobindo Pharma USA, Inc.¹¹³. In April 2015, over 8 tonnes of Amoxicillin clavulanate potassium were shipped from Aurobindo's Unit VII directly to U.S. pharma distribution giant McKesson, whose major customers include the retail giant CVS¹¹⁴. The combination of Amoxicillin and clavulanate potassium is used to treat a range of different infections, such as sinusitis, pneumonia, ear infections, bronchitis, urinary tract infections, and infections of the skin. Aurobindo's Units III, V, and XII in Bachupally, and its Unit VI in Chitkul also frequently export antibiotics to McKesson. All of these plants are located a short distance away from the critically polluted industrial area of Patancheru on the outskirts of Hyderabad, described in Part 2 of this report.

Aurobindo also has numerous links with EU markets both through its own subsidiaries and through drugs supplied to third parties. In France, for example, Aurobindo products are sold under the brand name Arrow Génériques, while in the UK they are marketed under various brands including Milpharm Ltd., Actavis, Arrow, and Aurobindo. Across Western Europe (specifically in France, Italy, Spain, Portugal, Belgium, Germany and the Netherlands) it sells Indian-manufactured drugs under the Actavis brand¹¹⁵, following its purchase of Actavis' European operations in 2014 – although some of those brands have since been merged with others. This is the case of Arrow Génériques, for example, which has superseded Actavis France. Through these different brands, Aurobindo markets its products to many large purchasers of antibiotics, including the UK's National Health Service and French hospitals¹¹⁶.

Through information gained from freedom of information (FOI) requests filed in summer 2016, it was revealed that Milpharm, Actavis, Arrow, and Aurobindo-branded antibiotics are being purchased by Barts Health and Cheshire & Wirral Partnership NHS Trusts. For example, Barts Health NHS Trust has Milpharm (for Cefalexin, Co-Amoxiclav, Flucloxacillin, and Valaciclovir) among its listed suppliers. The Cheshire and Wirral Partnership NHS Trust purchases Co-Amoxiclav from Aurobindo, as well as Cefalexin from Arrow Generics.

In addition to sales of its own branded drugs, Aurobindo also exports APIs to third party importers in the EU. For example, its Unit I facility in Medak District, on the outskirts of Hyderabad, appears in EU import registrations for the antibiotic Cefuroxime issued to companies based in Greece, Cyprus, and Poland¹¹⁷.

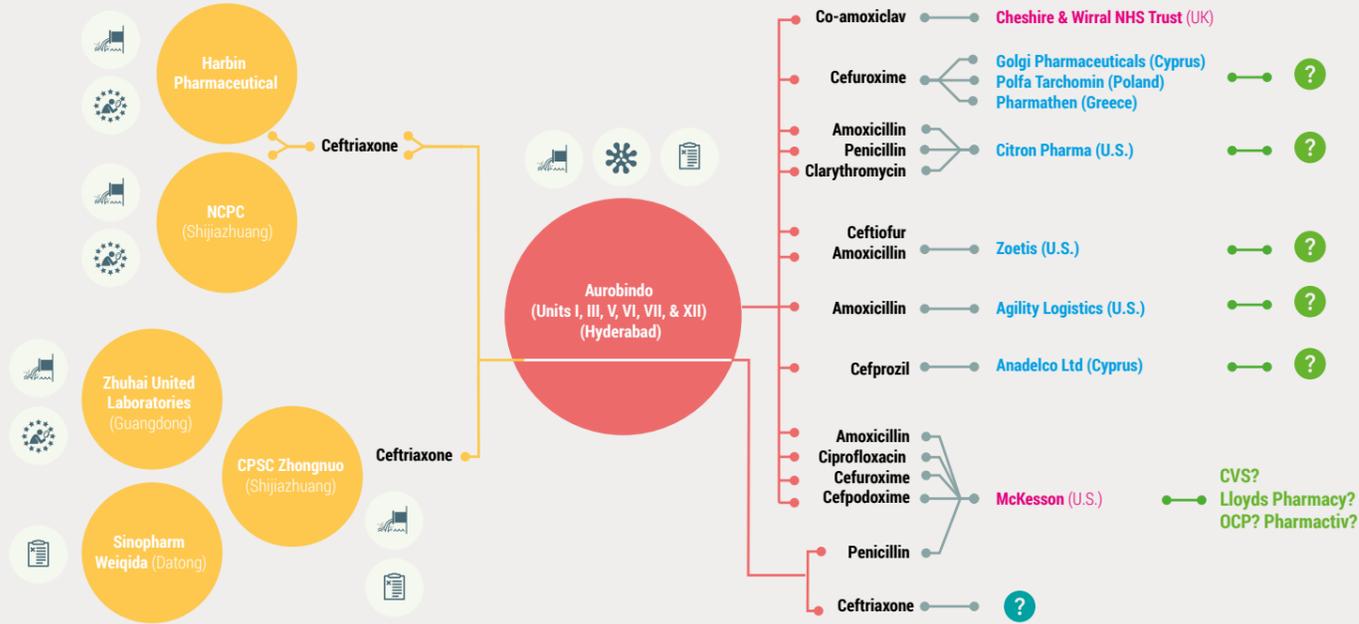
For the sake of brevity, other supply chain links are summarised in the table on page 36.



a) Ciprofloxacin antibiotic manufactured by Aurobindo and marketed by Northstar Rx (a subsidiary of McKesson) for sale on the US market.
b) Metronidazole antibiotic manufactured at Aurobindo's Unit VII factory in Polepally, Hyderabad. This is marketed under Aurobindo's own brand and for sale on the US market

UNRAVELLING THE GLOBAL ANTIBIOTICS SUPPLY CHAIN

Information displayed here was obtained from a variety of publicly accessible sources including the European Medicines Agency's EudraGMP database, U.S. customs records and Indian import and export data. It must be noted that describing the full chain of custody where more than two countries are involved is impossible based solely on data available in the public domain. In cases where we have been able to establish that a Chinese factory (A) is supplying a specific API (e.g. Ceftriaxone) to an Indian company (B), and that Ceftriaxone is also being sold by (B) to overseas customers (C), this is indicated for illustrative purposes. However, we are unable to confirm that (A) is where the Ceftriaxone contained in the drug purchased by (C) originates.

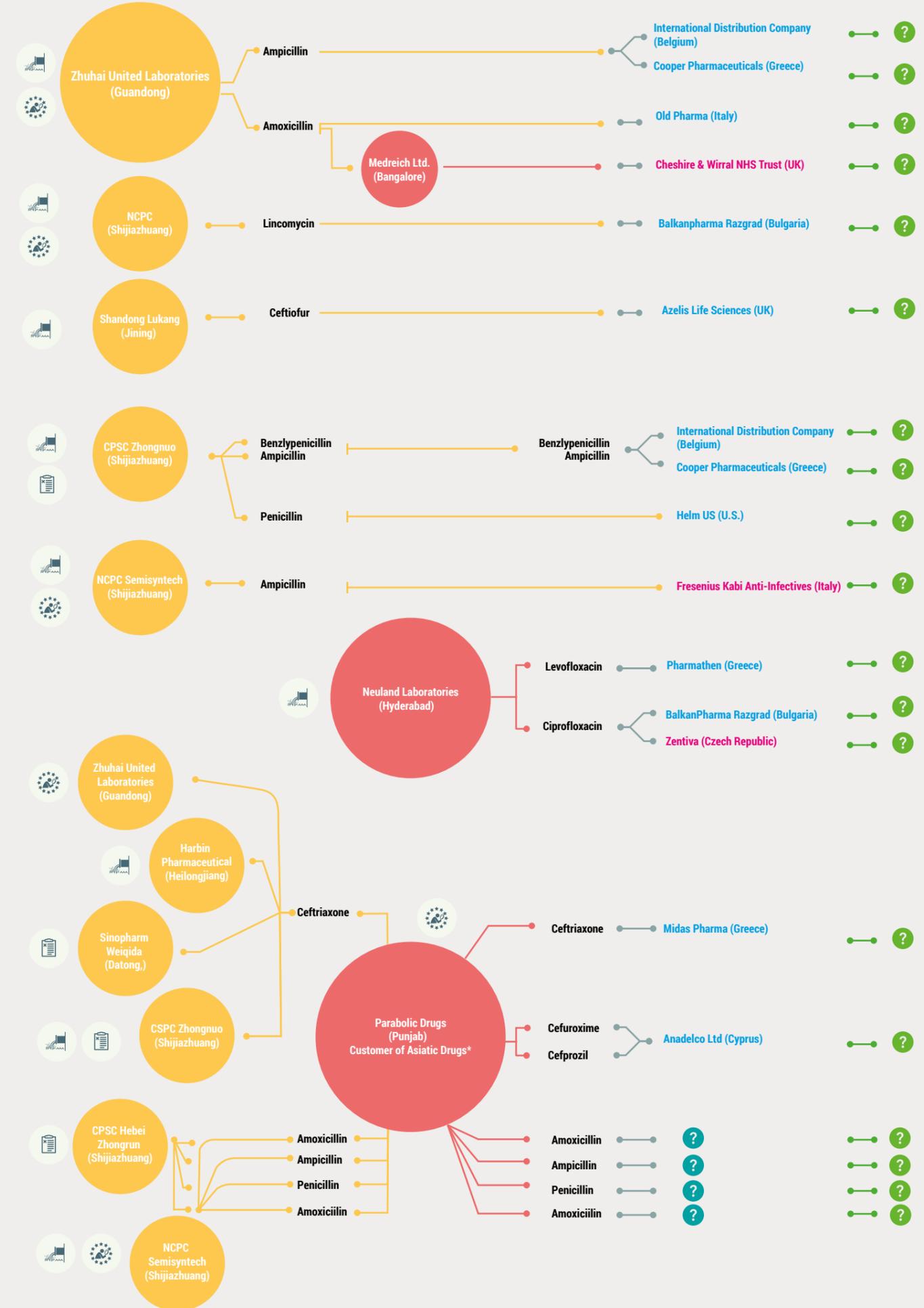
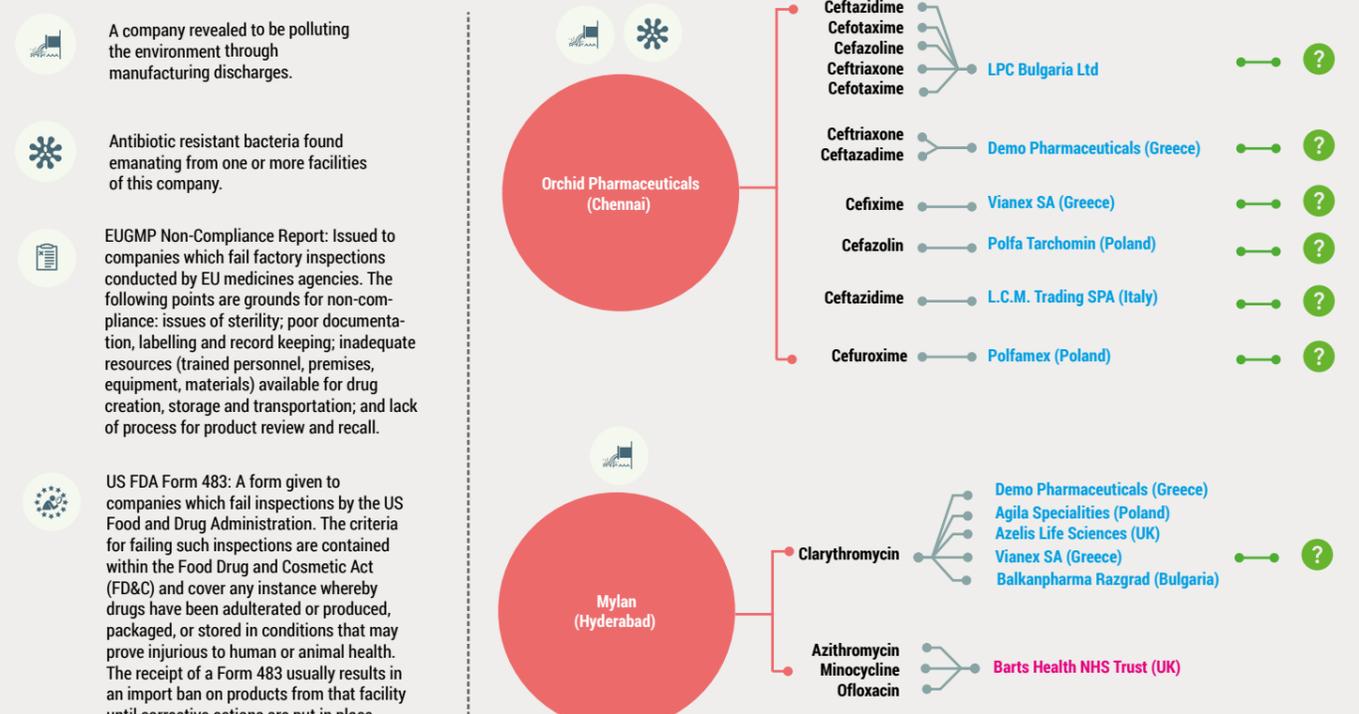
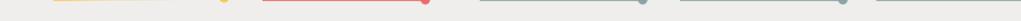
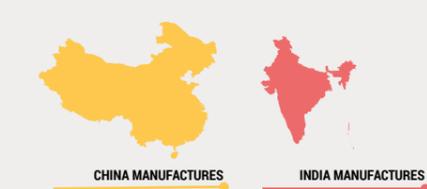


A company revealed to be polluting the environment through manufacturing discharges.

Antibiotic resistant bacteria found emanating from one or more facilities of this company.

EUGMP Non-Compliance Report: Issued to companies which fail factory inspections conducted by EU medicines agencies. The following points are grounds for non-compliance: issues of sterility; poor documentation, labelling and record keeping; inadequate resources (trained personnel, premises, equipment, materials) available for drug creation, storage and transportation; and lack of process for product review and recall.

US FDA Form 483: A form given to companies which fail inspections by the US Food and Drug Administration. The criteria for failing such inspections are contained within the Food Drug and Cosmetic Act (FD&C) and cover any instance whereby drugs have been adulterated or produced, packaged, or stored in conditions that may prove injurious to human or animal health. The receipt of a Form 483 usually results in an import ban on products from that facility until corrective actions are put in place.





Conclusion

This report has presented evidence of pollution scandals in India and China – two major suppliers of antibiotics and other APIs to global markets. An on-the-ground investigation in India has revealed extremely high levels of antibiotic resistance at pharmaceutical manufacturing sites, while detailed research and an investigation in China have uncovered failings in the GMP inspection system and a potential risk from the spread of antibiotic residues on soil in the form of fertiliser. Finally, we attempted to untangle part of the highly complex supply chain which links these reckless manufacturers in India and China with well-known companies whose branded drugs stock European and North American pharmacy shelves. Through our research, it also came to light that these manufacturers’ “own-brand” products feature in national drug databases throughout Europe and in the United States, and are being sold directly to hospitals, leading to the conclusion that public health services, which spend billions on treating people and fighting AMR, are channeling vast sums of money – directly or indirectly - to companies which are contributing to the spread of AMR through their negligent manufacturing practices.

With Governments around the world scrambling to contain the devastating and very costly damage that AMR is already wreaking on public health systems worldwide, urgent action must be taken to address every single man-made source of resistance, whether of human, animal, or industrial origin. If any one of these sources is left unaddressed, we will lose the fight against AMR.

When it comes to tackling antibiotic resistance, addressing pollution from the manufacturing of antibiotics is a low-hanging fruit. There is growing recognition of this: long an ignored cause of AMR, it is now accepted by decision-makers and leading industry players alike that manufacturing discharges must be brought under control as a matter of urgency.

In its December 2015 report *“Antimicrobials in Agriculture and the Environment: Reducing Unnecessary Use and Waste”* the Review on Antimicrobial Resistance identified pollution in the pharmaceutical supply chain as a causational factor in the spread of AMR and called on the industry to take measures to tackle it, also noting that “Major buyers of generic antibiotics could factor appropriate management of environmental considerations, including the amount of APIs and antibiotics that the company or their suppliers generate as waste, into their procurement decisions”¹¹⁸.

In its response to the Review on Antimicrobial Resistance’s final report, published in May 2016¹¹⁹, the UK Government in September 2016 duly recommended the establishment of targets for maximum levels of antimicrobial API discharge associated with the manufacture of pharmaceutical products and urged pharmaceutical companies to improve monitoring of API emissions from directly-operated manufacturing facilities as well as those of third party suppliers, and support the installation of proper waste processing facilities to reduce or eliminate API discharge (see Box).

In another encouraging development, also in September 2016, a group of major pharmaceutical companies including AstraZeneca, GSK, Johnson & Johnson, Pfizer and Sanofi published an Industry Roadmap for Progress on Combating Antimicrobial Resistance, which listed measures to reduce the environmental impact from the production of antibiotics as its first priority (see Box). The CEO of one of the signatories of the Roadmap, DSM Sinochem Pharmaceuticals, sub-

sequently called for the industry to go further by committing to buy APIs only from manufacturers that do not pollute the environment and to introduce more transparency in the supply chain¹²¹.

These pledges represent a significant step in the right direction, but a lot will depend on their actual implementation, notably the speed with which they enter into effect and the transparency of the measures taken. All stakeholders must now move quickly to ensure that the already significant body of scientific evidence on manufacturing discharges and the development of AMR, and the alarming findings presented in this report are taken seriously and result in real change on the ground. With this in mind, a series of recommendations for action are set out below. Key actors with the ability to change the situation are: major buyers of antibiotics, including public health systems and pharmaceutical retailers; the pharmaceutical industry itself; institutional investors seeking to manage their assets responsibly; and policymakers in Europe, the United States and other regulated markets.



UK Government response to the Review on Antimicrobial Resistance

September 2016¹²⁰

Recommendation 3. Reduce the unnecessary use of antimicrobials in agriculture and their dissemination into the environment

Recommendation 3.6. *Global bodies/national governments and regulators should establish evidence-based, enforceable targets for maximum levels of antimicrobial active pharmaceutical ingredient (API) discharge associated with the manufacture of pharmaceutical products.*

Recommendation 3.7 *Pharmaceutical companies should improve monitoring of API emissions from directly-operated manufacturing facilities as well as those of third party suppliers, and support the installation of proper waste processing facilities to reduce or eliminate API discharge. Such efforts should be based in voluntary, transparent and auditable commitments, with a globally-consistent 'quality mark' applied to end products produced on 'environmentally responsible' basis.*



Industry Roadmap for Progress on Combating Antimicrobial Resistance

September 2016¹²²

1) We support measures to reduce environmental impact from production of antibiotics, and will:

- i. Review our own manufacturing and supply chains to assess good practice in controlling releases of antibiotics into the environment.
- ii. Establish a common framework for managing antibiotic discharge, building on existing work such as [the Pharmaceutical Supply Chain Initiative - PSCI¹²³], and start to apply it across our own manufacturing and supply chain by 2018.
- iii. Work with stakeholders to develop a practical mechanism to transparently demonstrate that our supply chains meet the standards in the framework.
- iv. Work with independent technical experts to establish science-driven, risk-based targets for discharge concentrations for antibiotics and good practice methods to reduce environmental impact of manufacturing discharges, by 2020.

Signatory companies:

- Allergan
- AstraZeneca
- Cipla
- DSM Sinochem Pharmaceuticals
- F. Hoffman-La Roche Ltd., Switzerland
- GSK
- Johnson & Johnson
- Merck & Co., Inc., Kenilworth, New Jersey, U.S.A.
- Novartis
- Pfizer
- Sanofi
- Shionogi & Co., Ltd.
- Wockhardt



RECOMMENDATIONS FOR POLICYMAKERS

Regulators are increasingly focused on adopting a “one health” approach to public health in recognition of the fact that many factors affect human health. Environmental issues such as pharmaceutical pollution, and in particular its contribution to AMR, must not be overlooked. The European Commission has published several studies showing that pharmaceutical pollution is a significant problem for ecosystems and human health, but at the time of writing in September 2016, there is still no sign of its Strategic Approach to pharmaceuticals in the environment, which was initially slated for publication in 2015.

Legislators in Europe and the United States should:

- Include environmental criteria aimed at curbing manufacturing pollution in the GMP framework. In its December 2015 report, the Review on Antimicrobial Resistance recommended that GMP could potentially set maximum limits for concentrations of common antibiotics in water, which is the approach now being advocated by the UK Government (see Box). In addition to this, inspections under GMP rules should be significantly strengthened, so that factories that fail to implement them lose their access to global markets. GMP rules are largely harmonised and cover all companies importing APIs and other pharmaceutical products into the EU and U.S.;
- Demand more transparency in the pharmaceutical supply chain by asking companies to disclose the origin of their drugs right back to the factory that produced the raw materials. This would not only serve to improve production practices, but it would also contribute to better patient safety by ensuring total traceability of all pharmaceutical products throughout the supply chain.
- Make public support and investment in research and development of new antibiotics, as called for by the pharmaceutical industry in January 2016¹²⁴, conditional on companies’ commitment to clean production at their existing units and throughout their supply chain.

RECOMMENDATIONS FOR MAJOR BUYERS OF ANTIBIOTICS

- Blacklist pharmaceutical companies which are contributing to the spread of AMR through irresponsible manufacturing practices;
- Demand that the pharmaceutical industry clean up its supply chain and introduce greater transparency on the origin of antibiotic drugs;
- Review ethical procurement policies with a view to embedding environmental/AMR criteria in contractual requirements;
- Review all related procurement levers, including supplier codes of conduct with a view to mainstreaming environmental/AMR criteria across all relevant policies;
- Promote legislation to incorporate environmental criteria into Good Manufacturing Practices (GMP).

RECOMMENDATIONS FOR PHARMACEUTICAL COMPANIES

- Demand that all suppliers have in place effective measures to prevent and control pollution and to improve waste management standards. This should include dedicated waste water treatment and other measures to minimise waste from production processes, including the implementation of a maximum limit for concentra-



*A dead tree stands in flooded land near Thanam village.
In the distance is the Jawaharlal Nehru Pharma City, near Visakhapatnam*

tions of common antibiotics in water;

- Embrace full transparency and promote the transfer and adoption of cleaner production technologies and pollution prevention policies across the supply chain. This is something that is already a feature in other industries, including electronics and textiles. For example, many clothes retailers have introduced greater transparency in their supply chains in the wake of the Rana Plaza disaster in Bangladesh in 2013, including the public listing of the factories from which they source apparel¹²⁵.
- Fully participate in the development and data collection process of independent initiatives that increase corporate transparency and enable the diffusion of good practices, such as the upcoming AMR Benchmark produced by the Access to Medicine Foundation¹²⁶.

RECOMMENDATIONS FOR INVESTORS

The responsible investment community can play a vital role in holding pharmaceutical companies to account and putting pressure on the industry to stamp out pollution in its supply chains. Key demands from investors which would bring about a change of culture within the industry include:

- Require full disclosure from pharmaceutical companies in their portfolio regarding the identity of suppliers they source their APIs and other drug products from;
- Require that these companies have in place a detailed supplier responsibility programme with measurable environmental targets which provide an objective benchmark with which to rate and compare supplier performance;
- Divest from companies and producers involved in pollution scandals and require that all of the companies in their portfolio blacklist any pharmaceutical suppliers which do not comply with the standards set out in the supplier responsibility programmes.

Pharmaceutical pollution poses a grave threat to human health and ecosystems everywhere. With the consumption of medicines set to increase steeply in the coming decades, rapid and decisive action is required to nip what is still a relatively manageable problem in the bud. Given the global dimension of the AMR crisis, antibiotic pollution presents a clear priority area and should spur the international community and drug makers on to take swift action to address this aspect. However, in the longer run, what is required is a comprehensive, globally integrated response to all varieties of pharmaceutical pollution. History shows us that failure to act on scientific advice stores up major trouble for the future. We still have an opportunity to bring the pharmaceutical pollution crisis into check and prevent it from spiralling out of control.



Residents in Tikkavanipalem - a village downstream of the Jawaharlal Nehru Pharma City near Viaskhapatnam - collect water from the polluted local borewell. Despite having a water filtration plant in the village it was too expensive for many of the villagers to use, and has since broken anyway. The village's 400 families have now no choice but to use this one pump for their water. Reported issues associated with drinking with water include: bleeding and miscarriages amongst women, jaundice, asthma, stomach problems (particularly affecting children), cancer, and an increase unexplained mortalities

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