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# Understanding the antibiotic manufacturing ecosystem

A view of global supply chains, pressure points, and implications for antimicrobial resistance response

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# EXECUTIVE SUMMARY

## Context and objectives

Antibiotics are one of the greatest scientific breakthroughs of the 20th century, saving hundreds of millions of lives. However, a century after the discovery of penicillin, increasing antimicrobial resistance (AMR) has become a critical public health concern.

Many factors across the One Health spectrum, which recognises the interconnection of human and animal health as well as the environment, can contribute to the emergence and spread of antimicrobial resistance (AMR). In an environmental context, AMR risk arises when antibiotics enter the environment via human, agricultural and manufacturing sources, exposing bacteria to selective pressure.

Manufacturing presents a source for potential release of antibiotics into the environment, and currently no specific global standard or regulation exists for antibiotic levels in manufacturing effluent. Hence, there is growing interest in options to limit AMR risk from manufacturing waste, for example through introduction of further guidance or regulation to treat antibiotic manufacturing effluent prior to discharge.

However, there are gaps in the evidence-base on this issue that need to be addressed to guide any action taken by policy-makers. The introduction of any measures requiring significant investments from manufacturers could potentially disrupt certain supply chains, and with this affect the availability and affordability of medicines. Therefore, if such measures to limit antibiotic discharge are to be considered, it is important to understand the current state of the antibiotic supply chain, its fragilities and the impact on supply dynamics any potential measures may have.

The objectives of this study were three-fold:

1. Provide a high-level mapping of global antibiotic supply chains, key pressure points and fragilities to inform decision-makers on the current situation

2. Understand the impact of plausible environmental regulatory options on the overall antibiotic ecosystem, but also on select individual supply chains

3. Discuss options to ensure potential measures to limit antibiotic discharge from manufacturing effluent are introduced in a supply chain sensitive way

## Key results

The analysis focused on active pharmaceutical ingredient (API) manufacturing, and to a lesser extent intermediate[1] manufacturing (stage prior to API manufacturing), as these are often the bottlenecks of the supply chain. Additionally, the API stage poses the highest risk of antibiotic discharge into the environment during the manufacturing process.

Overall, there is limited vertical integration across the antibiotic supply chain, with various manufacturing stages often outsourced. This means an antibiotic consumed or used by a patient or animal will have involved manufacturing efforts by multiple different companies. Additionally, the antibiotic supply chain is significantly reliant on China and India, particularly at the API and intermediate stages:

- For a representative shortlist of 40 antibiotic APIs, close to 70% of the manufacturing sites are found in these two countries: 35% in India and 34% in China
- China is the largest exporter of antibiotic APIs in the world, with 74 kilotonnes exported in 2020, accounting for 71% of global inter-regions exports (across all antibiotic APIs)
- Intermediate manufacturing is particularly reliant on China, with more than 65% of the sites manufacturing four key intermediates[2] based in China.

A representative shortlist of 40 antibiotics was used to further characterise the impact of environmental measures on the antibiotic supply chain. Here, three antibiotic supply chain archetypes in terms of resilience of the API stage to new environmental regulation were identified. These archetypes may equally be relevant to other forms of change or disruption in the supply chain.

1. ***Supply chains resilient to new environmental regulation due to a high number of API manufacturing sites:*** mainly includes first-line generics with high demand. These have relatively low margins, but a high number of manufacturing sites – often geographically spread – which can reinforce supply if any sites are disrupted.

2. ***Supply chains with limited disruption risk from new environmental regulation due to high API margins:*** includes patented molecules, which have a limited number of manufacturing sites but high margins which gives manufacturers greater ability to absorb change.

3. ***Supply chains exposed to heightened risk from new environmental regulation due to low margins and limited number of API manufacturing sites:*** includes mainly antibiotics treating niche indications and last resort generics. These have low-to-medium margins and a small number of often geographically concentrated manufacturing sites which leaves manufacturers less able to absorb change and the supply more open to disruption if any sites stop manufacturing.

To better understand the impact of regulation both at a macro level and on select individual supply chains, two plausible environmental regulatory options that have been linked to current avenues of interest by policy makers for implementation were characterised. The two options differ in concentration limits, measuring location, and monitoring method:

- *Option A:* based on the AMR Industry Alliance Manufacturing Framework guidelines, entails antibiotic concentrations to be measured in the "mixing zone" after dilution (e.g., river water) and quantified via mass balance (whereby one calculates the amount of lost material by accounting for material entering and leaving the system) against set concentration limits

**[1] Note that only some intermediates will display structural antimicrobial activity**
**[2] 6-APA, an intermediate for the production of key antibiotics such as amoxicillin and ampicillin, 7-ACA an intermediate for cephalosporins antibiotics including ceftriaxone and cefuroxime, erythromycin used in the production of macrolide antibiotics including clarithromycin & azithromycin, and tetracycline used in the production of tigecycline.**

– *Option B:* based on the Indian government's draft 2020 regulation which was subsequently dropped, is overall more stringent than Option A. It has lower (i.e. stricter) antibiotic concentration limits than Option A and requires analytical monitoring (e.g. via mass spectrometry) of the antibiotic levels in the effluent wastewater before dilution.

If all incremental costs to implement these options were absorbed by the API and drug product (DP) manufacturers, it is estimated that Option A would have a very limited impact on manufacturers' annual profit pool (~$80M cost impact across all antibiotics, implying ~4% decrease in profit), whilst Option B could have a potentially more significant impact on annual profits (~$250M cost impact, implying ~12% decrease in profit).

Hence, Option B, while on average likely manageable, could potentially lead some manufacturers to leave the market and cause disruptions in supply chains that have a low number of suppliers. In such instances, there is a chance that Option B could potentially lead to short (3 to 6 months) and medium (6 to 24 months) term supply disruptions in 25-35% of the 40 molecules shortlisted, mainly in antibiotics treating niche indications and last resort generics. Any supply chain disruption could impact antibiotic availability and access, forcing doctors to rely on suboptimal treatment options and ultimately affecting patient outcomes. Hence, these more fragile supply chains would potentially require mitigating measures (e.g. additional implementation time, incentives, etc.) in such a scenario.

On the other hand, if all incremental costs were passed on to the market, they would on average represent less than a one percent price increase in both options. While the price impact is overall limited in both instances, this does not preclude high price increases of some specific antibiotics, and the disproportionate impact of any price increases on low-and-middle-income countries (LMICs).

In reality, a situation between these two extreme scenarios would be most likely, with some costs absorbed by manufacturers and some passed on to the market. In more competitive markets, suppliers are likely to have to absorb costs, but these supply chains have generally limited risk of disruption due to the high number of manufacturing sites. In supply chains with limited suppliers, the risk of disruption could be mitigated by the suppliers' bargaining power and their ability to pass on costs. However, investments would likely occur before price increases can be passed onto the market and thus may not reduce the risk of disruption in a meaningful way.

## Conclusions and Recommendations

Overall, this analysis suggests that measures to limit antibiotic discharges are viable and it is justifiable for policy makers to focus on addressing this issue. Of course, within any policy activity the impact on accessibility and availability of certain, often critical, antibiotics must be central. To ensure a proportionate response, balance will have to be struck between AMR risk from antibiotic discharge during manufacturing and the way in which any environmental measures are implemented, especially for the more fragile supply chains that were identified in the analysis.

To protect fragile supply chains, policymakers must carefully reflect on how to construct and implement measures to limit antibiotic discharge from manufacturing, and consider:

- 'What' regulatory measures should be, including the scope of antibiotics covered, the concentration limits for each antibiotic, where the concentrations should be measured, and which testing and monitoring methods should be used

- 'How' to implement these measures, including whether the approach is regulatory or otherwise, the timeframe, if complementary supporting measures will be used in parallel, and how to enforce compliance

- 'Who' should enforce the measures, which could include international bodies, national health or environmental regulators, procurement agencies or be voluntary

To minimise the risk to the antibiotic supply chain, regardless of the approach, it is recommended that policy makers ensure:

1. Discharge limits are evidence-based, ideally agreed on by an independent scientific advisory committee with broad and varied representation, drawing on input from industry

2. Clear, standardised, methods are available for measuring and monitoring discharge, including agreement on where and when measurement should take place

3. Cost-efficient processes to meet and monitor standards are available, putting in place guidelines on how to meet the regulated limits so stakeholders can be reassured that requirements are achievable in a cost-efficient way

4. Ambitious timeframes for implementation are set with industry input to ensure that these are realisable, and that sufficient implementation time is allowed to adapt to the measures

5. A tiered approach is considered based on the fragility of the supply chain, tailoring the measures (e.g. by archetype) and/or introducing additional supporting measures (e.g. adjusted implementation time, specific financial incentives etc.) for supply chains with higher risk of disruption, particularly those for critical antibiotics that have few or no alternatives

6. International implementation and coordination to realise the highest impact, promoting supporting actions that can be taken by countries who are net importers, and mitigating impacts for low- and middle-income countries

Particularly considering internationally coordinated options, three possible paths to action for how supply-chain sensitive approaches to AMR-driven environmental measures in manufacturing could be advanced are put forward. There is merit in relevant actors starting to examine feasibility of these different options in parallel to generate more evidence for which type of track may be most appropriate.

- Updated WHO Good Manufacturing Practice (GMP) guidelines implemented via national health regulators: *Discharge limits included in WHO GMP guidelines and then monitored by national health regulators*

- G20 environmental agreement implemented through national environmental regulation: *Discharge limits incorporated into G20 countries' environmental legislation and compliance monitored by national environmental agencies*

- G7/G20 sustainable procurement implemented through national/local procurement agencies: *G7 or G20 coordinated effort with discharge standards included in the selection criteria and implemented by national / local procurement agencies*

## Glossary

| Acronym | Definition |
|---|---|
| 7-ACA | 7-Aminocephalosporanic Acid |
| 6-APA | 6-Aminopenicillanic Acid |
| AMF | Access to Medicine Foundation |
| AMR | Antimicrobial Resistance |
| API | Active Pharmaceutical Ingredient |
| BPG | Benzathine Penicillin G |
| CAPEX | Capital Expenditure |
| cGMP | Current Good Manufacturing Practice |
| CMO | Contract Manufacturing Organisation |
| COGS | Cost of Goods Sold |
| DP | Drug Product |
| EMA | European Medicines Agency |
| EPA | (US) Environmental Protection Agency |
| EU | European Union |
| FDA | (US) Food & Drug Administration |
| GC-MS | Gas Chromatography-Mass Spectrometry |
| GMP | Good Manufacturing Practice |
| IV | Intravenous |
| LC-MS | Liquid Chromatography-Mass Spectrometry |
| MIC | Minimal Inhibitory Concentration |
| OPEX | Operating Expenditure |
| OSD | Oral Solid Dose |
| PNEC | Predicted No Effect Concentration |
| SC | Supply Chain |
| UN | United Nations |
| US | United States |
| WHO | World Health Organization |

# CONTEXT AND OBJECTIVES

Antibiotics are one of the greatest scientific breakthroughs of the 20th century, saving hundreds of millions of lives by curing infections and becoming a critical tool for modern healthcare. However, a century after the discovery of penicillin, increasing antimicrobial resistance (AMR) has become a critical public health concern. New data has revealed that at least 1.27 million deaths per year are directly attributable to antimicrobial resistance, and previous estimates suggest a cost to the global economy of US $100 trillion by 2050 [1] [2]. Moreover, the current pipeline of new and innovative antibiotics is very limited.

A One Health perspective highlights that many factors spanning human and animal health as well as the environment contribute to the emergence and spread of AMR. In an environmental context, AMR risk arises when antibiotics enter the environment via hospital, municipal and agricultural sources, and during the manufacturing process, exposing bacteria to selective pressure [3] [4].

In the case of manufacturing, relatively high levels of antibiotics in the environment can arise as a result of effluent discharge from manufacturing sites, leading to the contamination of nearby water sources with antibiotic residues [5]. Several studies have found antibiotic levels above the Predicted No Effect Concentration (PNEC), the concentrations above which antimicrobials are thought to apply a selective pressure for resistance, in river water near antibiotic manufacturing sites, and sometimes at levels exceeding those found close to hospital and municipal sites [3] [6] [7] [8].

Additionally, there are currently no formal global standards or regulations for antibiotic concentration limits in pharmaceutical wastewater, for example, at a WHO Good Manufacturing Practices (GMP) level, US Food & Drug Administration (FDA) / European Medicine Agency (EMA) level or in any national legislation.

However, the movement to reduce antibiotic discharge from manufacturing is gaining momentum, with some manufacturers already setting their own waste standards on a voluntary basis, particularly members of the AMR Industry Alliance (see box 1 for further details) [9]. To minimize the risk of environmentally linked AMR more effectively, some stakeholders are calling for the implementation of additional guidelines or regulations to treat and monitor industrial waste prior to discharge. For example, in 2020, the Indian Green Ministry proposed a set of national standards for industrial effluents from antibiotic manufacturing [10]. Whilst this move was praised by many as a much needed and progressive step, some voiced concerns over certain aspects, particularly the way in which discharge limits were set. Consequently, in

August 2021 the Ministry dropped the specification of limits for antibiotic residues in manufacturing effluent (see box 2 for further details) [11].

Depending on the approach, any new measures to reduce antibiotics in manufacturing discharge might require upgrading treatment technology and monitoring of the wastewater. Regulations that demand significant investment from manufacturers may drive up prices and/or push some suppliers out of the market, which has the potential to disrupt supply chains and affect the global availability and affordability of antibiotics.

Striking the right balance will not be easy. Many antibiotic supply chains are fragile and at risk of disruption given the low profit margins and, in many cases, few manufacturers producing key active pharmaceutical ingredients (APIs). At the same time, antibiotic supply chains are generally opaque, complex and can vary over time, making it hard to fully appreciate what the global impact of any measures may be in practice.

Thus, decision makers will have to move carefully and anticipate the challenges and risks in developing environmental measures, including an understanding of global supply chains (from sourcing of starting materials to packaging and distribution), who is involved at each stage (whether large innovators, small generics companies or third parties), and the potential economic impact.

### Objectives

The objectives of this study were three-fold:

1. Provide a high-level mapping of global antibiotic supply chains, key pressure points and fragilities to inform decision-makers on the current situation

2. Understand the impact of plausible environmental regulatory options on the overall antibiotic ecosystem, but also on select individual supply chains

3. Discuss options to ensure potential measures to limit antibiotic discharge from manufacturing effluent are introduced in a supply chain sensitive way

## BOX 1

### AMR Industry Alliance manufacturing members set voluntary discharge limits

The AMR Industry Alliance's Industry Roadmap established a common framework for managing antibiotics discharges from manufacturing [12]. The Alliance's manufacturing members, who have signed up to the Roadmap, comprise 18 companies, including seven generics manufacturers [13].

The framework requires members to ensure that antibiotic concentrations in effluent discharge over a certain period of time are below the Predicted No Effect Concentration (PNEC), the concentrations above which antimicrobials are thought to apply a selective pressure for resistance [14]. The concentration of antibiotics is measured via mass balance in the "mixing zone" after dilution, e.g. in nearby rivers downstream of the manufacturing plant. The framework specifies that members must conduct facility audits at least every five years, including a risk assessment of antibiotic discharge [15].

At present, the AMR Industry Alliance data is self-reported and the Alliance releases a high-level assessment of progress every 2 years. The 2021 report shows that 88% of products manufactured at sites owned by Alliance members have been assessed against PNEC targets, with 87% of those products meeting targets [16]. 90% of Alliance members with antibiotic manufacturing sites also manufacture products at direct supplier sites and are asked to pass standards on to suppliers. In these cases, only 42% of products manufactured at supplier sites have been assessed against PNEC targets, of which 73% met the targets. Independent assessment of performance of individual AMR Industry Alliance members and details of their approach to environmental risk is available in the Access to Medicine Foundation 2021 AMR Benchmark [50].

## BOX 2

### India attempts to set antibiotic discharge limits

India is one of the largest antibiotic API producers globally (see next section). In 2020, the Green Ministry proposed a set of national standards for industrial effluents from antibiotic manufacturing [10]. The published draft legislation contained concentration limits for over 120 antibiotics in manufacturing effluents.

The proposed thresholds were more stringent than PNEC discharge limits (used by the AMR Industry Alliance Manufacturing Framework), by a factor in the range of 2.5-25x, and were to be measured directly in the wastewater stream rather than the receiving aquatic environment, hence before dilution.

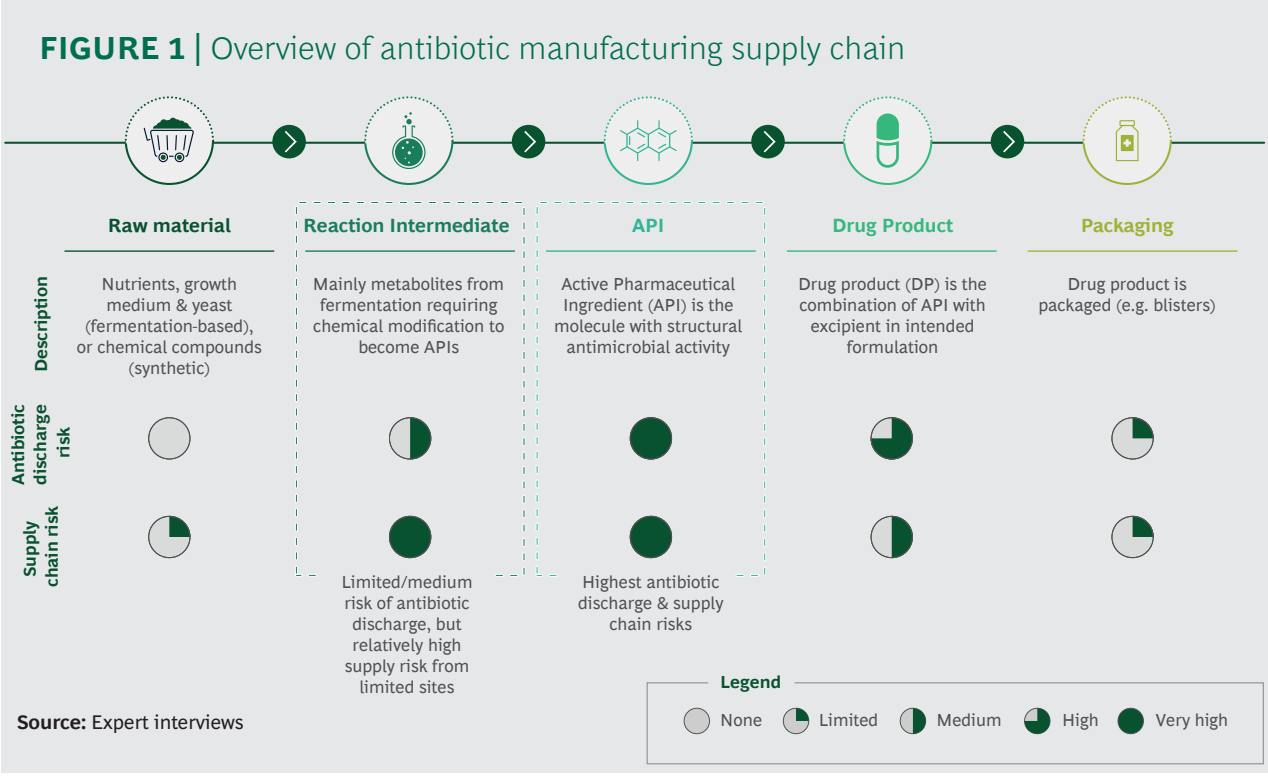
Whilst this move was praised by many as a much needed and progressive step, some voiced concerns over certain aspects. Particularly, Indian manufacturers believed the draft legislation would erode Indian competitiveness, that clear and cheap analytical methods to measure antibiotics in the waste effluent did not exist, and that the additional wastewater treatment costs could raise antibiotic prices. Consequently, in August 2021 the Ministry dropped the specification of limits for antibiotic residues in effluent wastewater [11].

# KEY FINDINGS

## Mapping the Antibiotic Supply Chain

A supply chain mapping was conducted, focusing on API manufacturing sites, and to a lesser extent reaction intermediates[3] (see Figure 1 for a schematic view of the antibiotic supply chain and role of each stage), as these are often the bottlenecks of the supply chain. Additionally, the API stage poses the highest risk of antimicrobially active discharge, given the high production volumes resulting in potentially high localised concentrations in the wastewater, and the fact that API production is often in liquid form, with heightened risk of migration to the environment.

**FIGURE 1** | Overview of antibiotic manufacturing supply chain



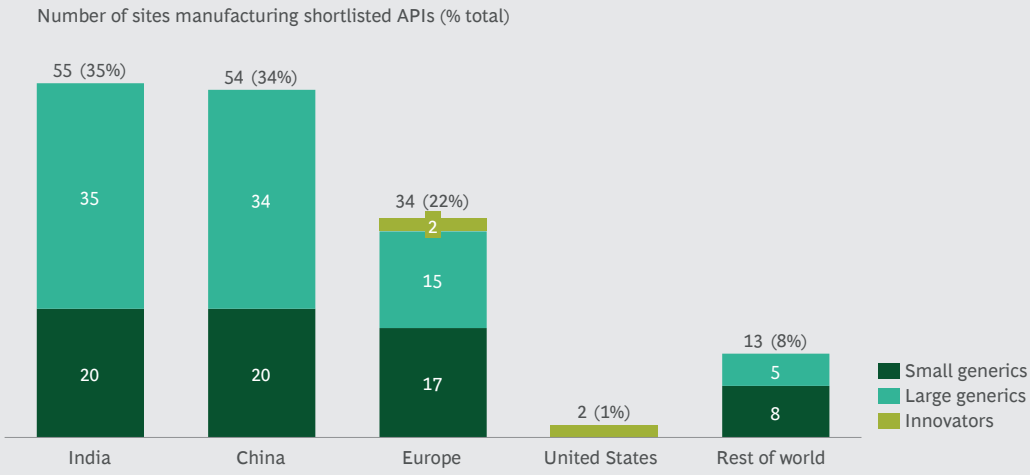

**Source:** Expert interviews

[3] **Note that only some intermediates will display structural antimicrobial activity**

To study the supply chain, a representative shortlist of 40 antibiotics was selected. The shortlist, although it mainly included generic antibiotics also included six on-patent molecules. It had broad representation across a wide variety of different pharmacological properties, resistance levels, formulations and manufacturing techniques (see Appendix for full list). It is worth noting that the analysis represents a snapshot in time (as-of November 2021), and while macro-level trends in the supply chain take time to develop, individual changes at an API and manufacturer level can be rapid.

Over the past few decades, API manufacturing has moved from the USA and EU to India and China due to their lower production costs. The two countries are home to nearly 70% of sites manufacturing the 40 shortlisted APIs, India representing 35% and China 34% (see Figure 2). While the number of manufacturing sites is similar between the two countries, the volumes produced per site in China are generally two to three times higher than sites in India. Europe has retained some API manufacturing, representing 22% of sites producing the shortlisted 40 molecules, but most of the API production has shifted out of the United states with only two API manufacturing sites present. Additionally, while some pharmaceutical innovator companies still sell antibiotics, very few continue to make APIs, and instead they outsource production to generics manufacturers. In general, limited vertical integration was noticed with often several stages of the manufacturing process outsourced by market authorisation holders [17].

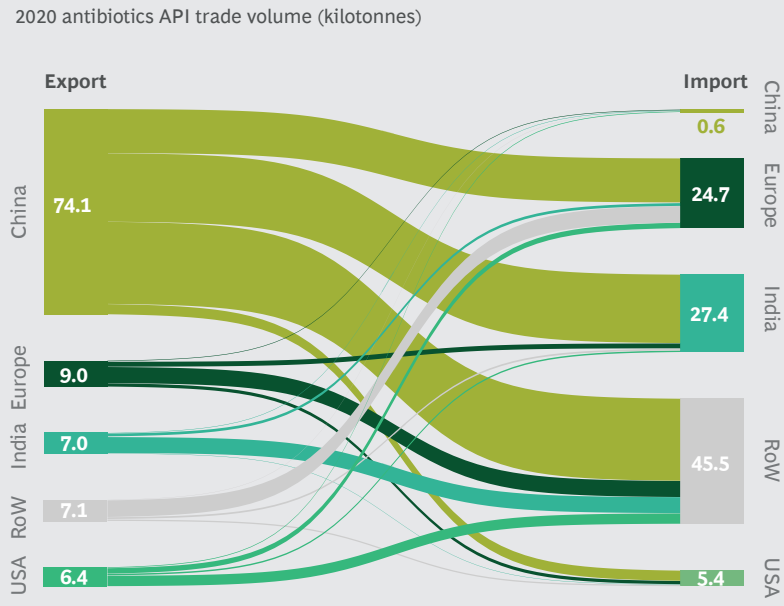
**FIGURE 2** | Global overview of sites manufacturing representative 40 antibiotic APIs




**Source:** Clarivate's Cortellis API database supplemented with BCG analysis

Moreover, China is the largest API exporter (71% or 74.1 kilotonnes in 2020), with Europe and India being the largest API importers as large drug product (DP) manufacturers (24.7% and 27.4% respectively, see Figure 3). While the United States are the second largest antibiotic market by revenue after the Asia-Pacific region (combining India and China), the country imports most of its antibiotics in finished goods [18].

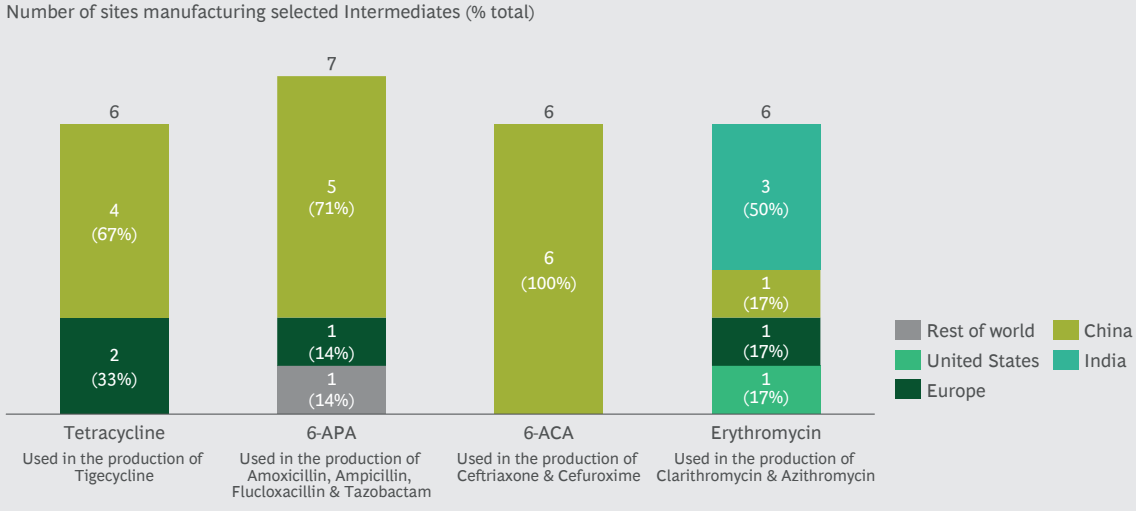
## **FIGURE 3** | Overview of globally exported API volumes




**Source:** IHS Markit (2020); API IHS Code – all 2941 H6 codes

The reliance on Asia and particularly China is even more apparent at the reaction intermediate stage for certain antibiotics (see Figure 4). 71% of manufacturing sites for 6-APA, an intermediate for the production of key antibiotics such as amoxicillin and ampicillin, and 100% of sites manufacturing 7-ACA, a key intermediate for cephalosporins ceftriaxone and cefuroxime, are based in China.

## **FIGURE 4** | Site location for key intermediates in antibiotics manufacturing




**Source:** Clarivate's Cortellis Intermediate database supplemented with BCG analysis

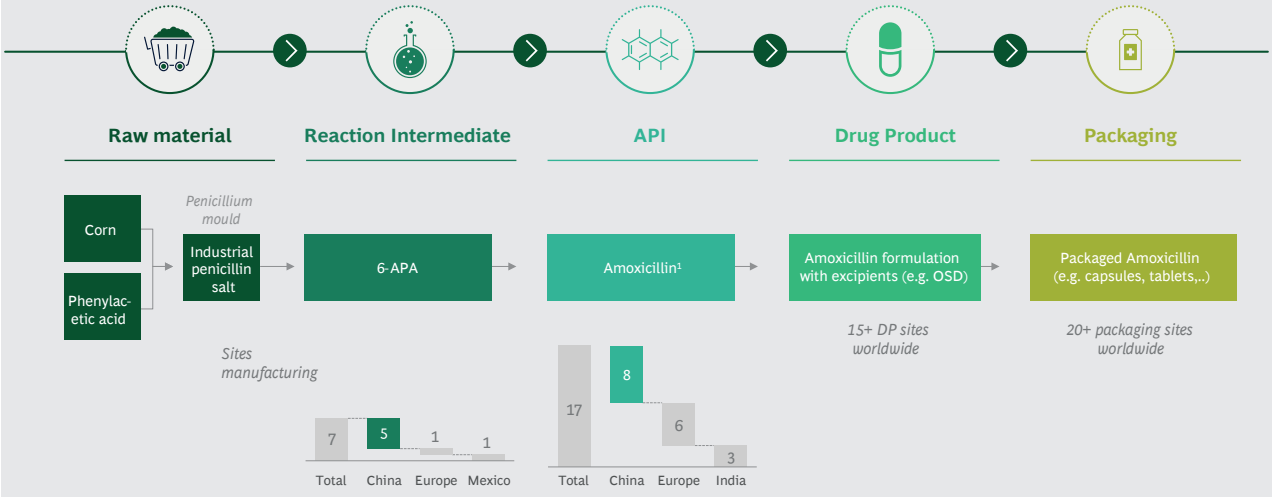
This supply chain mapping shows the reliance on China and India for antibiotic supply manufacturing, especially at the API and intermediate stages. Any potential measures put in place to limit antibiotic discharge during the manufacturing process should take this geographical dependency into consideration, as well as the increased pressure to reduce costs that has caused manufacturing to move to these countries.

## BOX 3
### Case example – Amoxicillin

Even high-volume generic antibiotics such as amoxicillin have potential supply chain fragilities, particularly at the intermediate stage.

Amoxicillin is produced through a semi-synthetic manufacturing process (see Figure 5). There are 17 sites manufacturing the amoxicillin API. Of those, six are located in Europe, three in India and eight in China. This would seem to indicate a broadly dispersed geographic manufacturing capability. However, there are only seven sites in the world estimated to currently manufacture the reaction intermediate 6-APA, and five of those are based in China. Therefore, any disruptions to 6-APA exports from China could put the supply chain of amoxicillin at risk.

**FIGURE 5** | End-to-end supply chain of amoxicillin




**Source:** Clarivate's Cortellis Intermediate and API database supplemented with BCG analysis

## The potential impact of environmental regulatory measures on the supply chain

The second part of the analysis focused on understanding the impact of plausible environmental regulatory options on the antibiotic supply chain overall as well as on select individual supply chains.

### *Factors that Influence Supply Chain Resilience*

Supply chain resilience for a given molecule is influenced by several factors, including:

- Manufacturing site number: An antibiotic with few API manufacturing sites has a supply chain that is generally more prone to externalities and micro-events and therefore has a higher risk of disruption

- Geographic location: The geographical concentration of manufacturing sites in a supply chain makes them more susceptible to disruption by events such as natural disasters or prone to geopolitical risk

- Manufacturer size: Smaller manufacturers are less able to absorb any additional costs due to their lower revenues, making them more sensitive to any infrastructure investments or additional running costs

- Manufacturer API portfolio: The more diverse (non-antibiotics) the API portfolio of the manufacturers, the more readily they can switch production to non-antibiotic APIs where additional investments are potentially not required and margins are more attractive

- Margins: The greater the profit margin of a molecule, the more room there is for cost absorption and the more worthwhile it is for a manufacturer to produce a molecule, and hence the more likely they are to continue manufacturing the molecule even if costs increase. The majority of antibiotics are off-patent, relatively low cost, and therefore likely to only attract low profit margins compared to on-patent drugs.

Using the above parameters to analyse the antibiotic supply chain, three supply chain archetypes were identified in terms of resilience to new environmental regulation (see Figure 6):

**Archetype 1 - Molecules resilient to new environmental regulation due to high number of API manufacturing sites:**

The molecules with the most resilient supply chains are often generics with high demand (e.g., azithromycin, ciprofloxacin). These molecules tend to have lower API margins compared to patented molecules, but their supply chains are relatively resilient due to a high number of API manufacturing sites (often over ten) that are geographically dispersed. Even if new regulations pushed some API manufacturers out of the market, it is likely that the remaining API manufacturers could step up production volume and/or new manufacturers could come into the market in the medium to long term to meet demand.

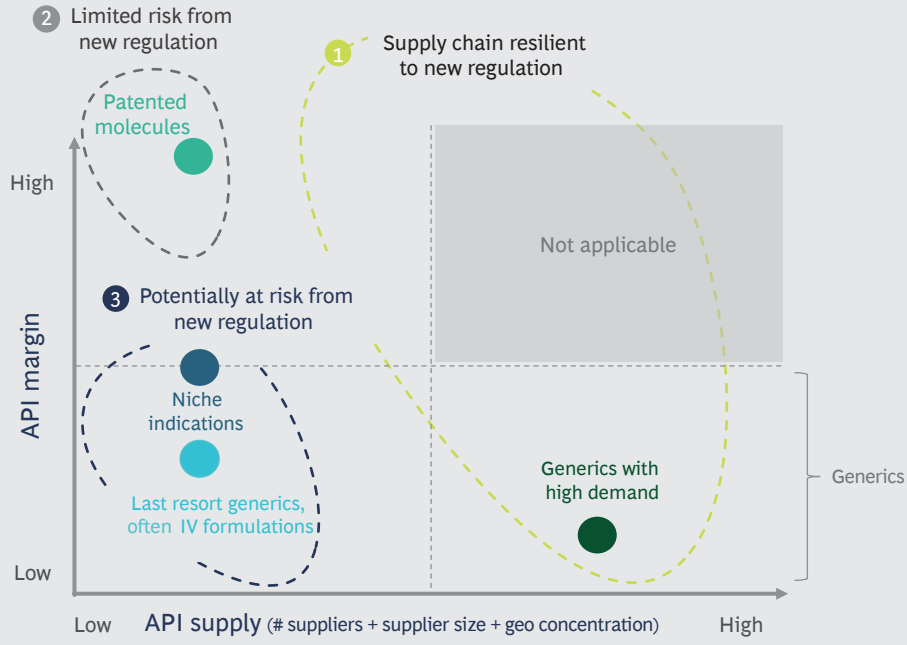
**Archetype 2 - Molecules with limited risk from new environmental regulation due to high API margins:**

Characterised by patented molecules, these supply chains often have few API manufacturing sites (one to three) but relatively high margins. While the low number of sites would suggest these supply chains are at risk of disruption, the relatively high margins and the reputational damage from stock-outs mean that the costs can be more readily absorbed and the patent-holding companies that control the supply chains try to ensure these are robust.

**Archetype 3 - Molecules exposed to heightened risk from new environmental regulation due to low margins and limited number of API manufacturing sites:**

The molecules with the most at-risk supply chains mainly include last resort generics which are often intravenous formulations (e.g. meropenem), and molecules treating niche indications (e.g. ertapenem). These APIs are manufactured at a small number of manufacturing sites (often less than six API sites) in two to four countries. Since these molecules have low to medium margins, manufacturers may be less inclined to make any investments required by new regulation and could potentially exit the market, especially in cases where antibiotics form only a small part of their portfolio. With so few API manufacturers, any exit could disrupt the supply chain.

**FIGURE 6** | Overview of the three supply chain archetypes in terms of resilience to new environmental regulation




**Source:** Expert interviews; BCG analysis

## Two plausible regulatory options to determine the impact of environmental regulation

To determine the potential impacts of additional environmental regulations on the supply chain, two plausible regulatory options that have been linked to current avenues of interest by policy makers for implementation were characterised. The two options differ in concentration limits, measuring location, and monitoring method:

- Option A: based on the AMR Industry Alliance Manufacturing Framework guidelines, entails antibiotic concentrations to be measured in the "mixing zone" after dilution (e.g., river water) and quantified via mass balance (whereby one calculates the amount of lost material by accounting for material entering and leaving the system) against set concentration limits (PNEC[4])
- Option B: based on the Indian government's draft 2020 regulation which was subsequently dropped, is overall more stringent than Option A. It has lower (i.e. stricter) antibiotic concentration limits than Option A and requires analytical monitoring (e.g. via mass spectrometry) of the antibiotic levels in the effluent wastewater before dilution

The analysis explored various economic and supply impacts assuming Options A and B were applied as formal regulations and implemented in all API and DP manufacturing sites globally.

**4 AMR Industry Alliance uses the Predicted No Effect Concentration (PNEC) as discharge limit. This is the concentration below which antimicrobials no longer apply a selective pressure for resistance**

*The macro-economic impact of environmental measures*

Through quantitative analysis and a series of expert interviews, it was estimated that implementing the additional wastewater treatment and monitoring required in Option A globally across all antibiotic API and DP manufacturers would likely lead to a ~2% ($80M) increase in annual running costs (costs including capital depreciation, utilities, labour, etc. but excluding raw materials). On the other hand, the increase associated with Option B would be ~7% ($250M) of annual running costs (see Appendix for further details).

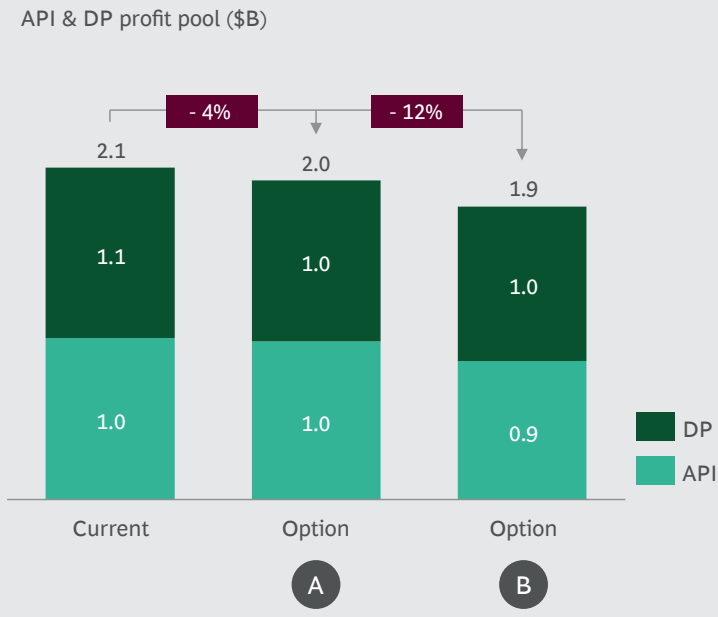
To explore the potential implications of these cost increases, two extreme scenarios were considered. The first scenario assumes that all costs are absorbed by the API and DP manufacturers, while the other assumes all costs are transferred to the market, pushing up market prices:

1. .Manufacturers absorb all additional costs

If manufacturers were to absorb all additional costs, Option A would represent a limited ~4% decrease in the $2.1B combined antibiotic API and DP manufacturers annual profit pool. However, Option B could potentially lead to a more significant impact with a ~12% decrease in annual profit (see Figure 7).

While the annual profit change in Option B is on average likely manageable, it could be significant enough to make some manufacturers leave the antibiotic market, particularly those who could quickly pivot to supply other categories of products where margins are more attractive and infrastructure change is not required. Where number of production sites is limited, which is the case for many niche indication antibiotics and last resort generics, loss of even one manufacturing site could impact supply. This would be felt most keenly by low- and middle-income countries (LMICs) who may be less able to pivot procurement approaches, forcing practitioners to rely on suboptimal or more expensive alternative treat-

**FIGURE 7** | Decrease in profitability across API and DP manufacturers assuming all costs are absorbed by manufacturers




**Source:** Expert interviews; BCG analysis

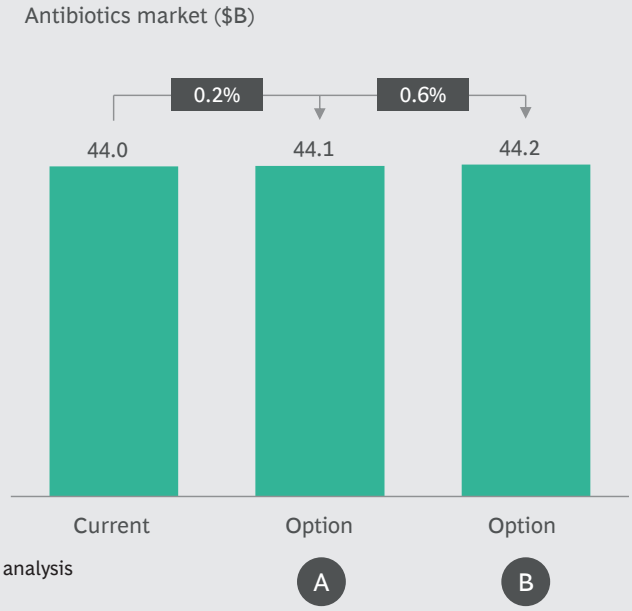
ment options and resulting in negative impacts on patient outcomes [19] [20].

2. Additional costs are transferred to the market

Alternatively, if additional costs due to regulation were to be absorbed by the end payer rather than the manufacturer, then antibiotic prices on average would likely increase by less than 1% under both Options A and B (see Figure 8).

While this overall price increase sounds very limited, there could be more significant price fluctuations on a molecule-by-molecule level as regulations may not affect all types of supply chains in the same way. At the same time, even small price increases will pose a disproportionate impact on access to antibiotics in LMICs, again pushing practitioners to prescribe suboptimal treatments and negatively impacting patients [19] [20].

**FIGURE 8 |** Increase in the antibiotics market value assuming all costs are transferred to the market




**Source:** Expert interviews; BCG analysis

Of course, a situation between these two extreme scenarios would be most likely, with some costs absorbed and some passed on. In general, in more competitive markets, manufacturers are more likely to have to absorb the costs due to the pressure to keep prices low. However, in such markets, even if some players were to leave, supply chains are at limited risk of disruption due to the high number of manufacturing sites. On the other hand, in supply chains with limited suppliers, the risk of disruption might be mitigated by the bargaining power of the manufacturers, whereby costs can more easily be passed on to customers. Though of course this could impact the affordability of certain antibiotics, especially in LMICs as described above. However, the investments to implement change would likely be required before any price increase can be passed onto the customer, and therefore the ability of a manufacturer to raise prices may not ultimately reduce the risk of disruption if companies choose not to invest in changes to manufacturing processes at risk. This disruption could have greater impacts on antibiotic availability and patient access in cases where manufacturing site number is most limited.

Even though it is difficult to pin-point which situation will occur, this macro view gives an initial indication of where potential impacts exist. It also shows that impacts on antibiotic accessibility are possible, particularly under regulatory Option B, so it is important to understand the impact on individual supply chains any regulation may have.

## Applying two plausible regulatory options to the 40 shortlisted antibiotics

Therefore, further analysis was conducted to assess which of the 40 shortlisted antibiotics would have supply chains at heightened risk of disruption under Option B.

Assuming all costs are absorbed by the manufacturers, analysis of supply chain resilience factors suggested an estimated 25-35% (10-15) of the shortlisted 40 antibiotics could be at heightened risk of disruption under Option B. These proportionally mainly include last resort generics and niche indication antibiotics (see Table 1). Within this group of molecules, there are different degrees of risk depending on key supply chain factors, including the number of API sites owned by small manufacturers, the concentration of API manufacturing sites located in a single country and the API portfolio of the manufacturer (see Box 2 for detailed examples).

Antibiotics seen to be at most risk correspond to "Archetype three" molecules (i.e. low margin APIs with a limited number of API manufacturing sites). They are at heighted risk of disruption if even one manufacturer were to leave the market. In these cases, while other suppliers would likely step in to fill gaps in supply as a result of any market exits, making these shortages temporary, it is estimated that it could take three to six months for existing manufacturers to ramp up API production. Should new manufacturers need to enter the market to make up lost supply, or existing manufacturers need to invest to increase capacity, disruption could even persist to the medium- term, for anywhere between six to 24 months. However, given the dynamic nature of supply chains it is hard to say exactly how likely such disruptions might be.

**Table 1** | Key features of the supply chains with potential increased risk of disruption from Option B, and two exemplary supply chains with limited increased risk

High demand
Niche
Last resort

| Archetype | Degree of additional risk | API | 1 Manufacturing sites: Nr. of sites | 2 Size: Small players | 3 Geographic concentration: Concentration in one country | 4 Switching likelihood: Sites w. potential to shift to other APIs due to portfolio | 5 Margin: Est. margins |
|---|---|---|---|---|---|---|---|
| Archetype 3 | High in ~25% of 40 shortlisted APIs | Minocycline | 4 | 3 (75%) | 2 (50%) | 3 (75%) | 10 - 15% |
| | | Metronidazole | 3 | 1 (33%) | 2 (67%) | 2 (67%) | 5 - 10% |
| | | Doxycycline | 4 | 4 (100%) | 1 (25%) | 4 (100%) | 5 - 10% |
| | | Nitrofurantoin | 4 | 4 (100%) | 1 (25%) | 4 (100%) | 5 - 10% |
| | | Ofloxacin | 4 | 3 (75%) | 2 (50%) | 2 (50%) | 15 - 20% |
| | | Trimethoprim | 4 | 3 (75%) | 3 (75%) | 2 (50%) | 15 - 20% |
| | | Tigecycline | 3 | 1 (33%) | 1 (33%) | 3 (100%) | 10 - 15% |
| | | Daptomycin | 4 | 2 (50%) | 2 (50%) | 2 (50%) | 10 - 15% |
| | | Sulfamethoxazole | 3 | 1 (33%) | 2 (67%) | 1 (33%) | 15 - 20% |
| | | Ertapenem | 3 | 1 (33%) | 1 (33%) | 0 (0%) | 15 - 20% |
| | Moderate in ~10% of 40 shortlisted APIs | Flucloxacillin | 4 | 0 (0%) | 2 (50%) | 1 (25%) | 5 - 10% |
| | | Gentamicin | 4 | 0 (0%) | 2 (50%) | 0 (0%) | 5 - 10% |
| | | Colistin | 5 | 2 (40%) | 3 (60%) | 1 (20%) | 10 - 15% |
| | | Tobramycin | 5 | 2 (40%) | 3 (60%) | 1 (20%) | 5 - 10% |
| | | Erythromycin | 6 | 3 (50%) | 3 (50%) | 2 (33%) | 5 - 10% |
| Archetype 1 | Limited in ~65% of 40 shortlisted APIs | E.g. Azithromycin | 16 | 5 (31%) | 6 (38%) | 8 (50%) | 5 - 10% |
| | | E.g. Ampicillin | 15 | 2 (13%) | 7 (47%) | 3 (20%) | 5 - 10% |

Additional risk of disruption

**Source:** Clarivate's Cortellis API database supplemented with BCG analysis; expert interviews

In the event of disruption and/or low supply of these molecules, healthcare professionals may need to prescribe alternative treatments which can be less effective or have a higher risk of side effects. This could also heighten AMR risk, especially where narrow spectrum antibiotics are substituted for broad spectrum [21]. However, for some indications, only one treatment is available and so supply disruption can severely impact patient outcomes and in the worst instances lead to death [19] [20]. In this situation, panic mass purchase or stockpiling by some buyers could make supply disruptions worse, putting low- and middle-income countries who do not have the funds to mass purchase at even more of a disadvantage.

## BOX 4

### Example antibiotics at heightened risk of supply chain disruption

***Sulfamethoxazole*** is used as a combination therapy together with Trimethoprim (Co-trimoxazole) in the treatment of certain infections, including Pneumocystis jiroveci pneumonia (PCP) and complicated urinary tract infections [22]. Globally, there is one API manufacturing site in China and two sites in India manufacturing the molecule. However, the two Indian sites are owned by the same Indian company and located in neighbouring states. Since the Chinese site is focused on domestic supply, the Indian supplier is responsible for more than 80% of the global sulfamethoxazole supply, putting the supply chain at risk of disruption from externalities.

***Ertapenem*** is a niche indication antibiotic used in the treatment of complicated intra-abdominal, urinary tract and skin infections, community acquired pneumonia, and acute pelvic infections [23]. Four API manufacturing sites capable of manufacturing ertapenem were identified– one in each of India, China, Taiwan and Italy. However, further investigation found that the site in India does not currently manufacture the sterile API, leaving only three sterile manufacturers in the market. If any were to reduce capacity in response to regulatory changes or other micro-events, the risk of supply chain disruption could be significant.

***Daptomycin*** is a lipopeptide semi-synthetic antibiotic on the reserve list of the WHO AWaRe classification for treatment of skin infections by S. aureus – a highly resistant pathogen [24] [25]. Six sites can manufacture the API, but only four are actively producing it. Of the active producers, two are in China and two belong to small European manufacturers. If the largest manufacturer in China were to leave the market, there could potentially be significant disruption.

# CONCLUSIONS AND RECOMMENDATIONS

## Conclusions of analysis

The supply chain mapping conducted shows that the antibiotic supply chain is characterised by a reliance on China and India, particularly for API manufacturing, and any measures to limit antibiotic discharges during the manufacturing process will need to take this geographical concentration into account. Additionally, there is limited vertical integration across the antibiotic supply chain, with some supply chains being inherently fragile due to the low number and the diversity of API and intermediate suppliers.

Economic analysis of the impact on the supply chain of measures to limit antibiotic discharge during manufacturing shows that these measures are on average likely manageable. However, the impact on some supply chains, including antibiotics with niche indications and last resort generics, could be more significant if stringent options were to be implemented. Such supply chains would likely need additional considerations, such as inclusion of supporting measures (e.g. additional implementation time, incentives, etc.).

Overall, this suggests that measures to limit antibiotic discharge are viable and it is justifiable for policy makers to focus on addressing this issue. Of course, within any policy activity the impact on accessibility and availability of certain, often critical, antibiotics must be central. To ensure a proportionate response, balance will have to be struck between AMR risk from antibiotic discharge during manufacturing and the way in which any environmental measures are implemented, especially for the more fragile supply chains that were identified in the analysis.

## Addressing the "What", "How" and "Who"

When considering any measures to limit antibiotic discharge during manufacturing there are a range of options that should be considered – "what" these measures might look like, different ways on "how" to implement them, and "who" will enforce them.

The question of "what" measures to implement includes (not exhaustively):

- Whether measures should cover the whole antibiotic business, only select stages and/or just certain types of molecules. For example, the measures could initially only target antibiotics with low risk of disruption, and then be broadened over time

- The standards for concentration limits that should be used, drawing from latest scientific evidence on AMR risk

- The measuring spot, which could be in the effluent 'waste pipe' where antibiotic concentrations will be highest and hence potential risk to AMR are likely highest, or in the 'mixing zone' (e.g. river water) after dilution which is the location used in most environmental legislation

As for "how" to implement environmental measures in manufacturing, there are several mechanisms available that could be used in isolation or in combination, including but not limited to:

- **Discharge limits in GMP guidelines:** GMP guidelines could be updated to include environmental factors such as specific limits for acceptable concentrations of antimicrobials in manufacturing effluent

- **Discharge limits in environmental regulation:** Environmental regulations could be updated to include concentration limits for antibiotics in manufacturing wastewater

- **Sustainable procurement:** Environmental factors could be included alongside price and quality in selection criteria, rewarding manufacturers who implement higher environmental standards with higher prices (see case study)

- **Voluntary discharge limits:** Coordinated standards implemented across industry on a voluntary basis

- **Sustainable reimbursement:** Delinked reimbursement models could allow fixed annual payment for critical antibiotics or additional annual payments, on top of revenues, for manufacturers adhering to environmental standards (see case study)

- **Financial incentives such as tax credits:** A tax incentive could reduce the amount of tax paid by manufacturers for updating their equipment to meet new environmental standards

- **Improving supply chain transparency:** Sharing (real-time) data regarding the name and location of suppliers throughout the antibiotics supply chain, as well as production volumes, provides a clearer view of supply chain dynamics and could enable better assessment of environmental impact of industrial discharge by identifying potential source points for polluting agents (see case study)

- **Publishing company performance:** Publicly sharing how companies limit environmental contamination or comply with discharge standards could incentivise good practice and even extend to suppliers, as companies seek to maintain a positive image throughout the supply chain

- **Issuing best practice guides:** Providing best practice guidelines on waste discharge could help move companies towards better practices even though they are non-binding

Several of these approaches, including the implementation of voluntary discharge limits by industry or the set-up of sustainable reimbursement model may benefit from the creation of a global third-party ISO-type standard so that actions by the manufacturers can be audited. It could be envisioned that such standards would be required by procurement agencies too.

Linked to the "how" of the implementation strategy, there are several options on "who" should enforce any measures, including but not limited to:

- International bodies such as the WHO (e.g. via GMP guidelines)

- National health regulators (e.g. FDA, MHRA and EMA)

- Environmental agencies (e.g. EPA)

- National or local procurement agencies (e.g. NHS)

- Industry directly (e.g. through the implementation of voluntary standards)

## BOX 5

### How to tackle antibiotic discharge from manufacturing: Country Case Studies

***Norway – Sustainable procurement***

In 2019, the Norwegian government started a pilot sustainable procurement programme in which antibiotic manufacturers are rewarded if they document good environmental practices [26]. Criteria for rewards consider a company's overall environmental policy, environmental strategy, and control system put in place to tackle environmental issues. In the antibiotic procurement decision-making process, 30% of the weighting is linked to the environmentally friendly production. If the pilot is successful, sustainable procurement criteria will be applied to other tendering processes.

***Sweden – Sustainable reimbursement***

In June 2018, the Swedish government launched a pilot study with four pharmaceutical companies and five patent-protected antibiotics to test a new reimbursement model [27]. Under the program, suppliers guarantee the availability of the selected antibiotic products through specified warehousing, and in return they receive a guaranteed annual income per product. If purchases of those antibiotics fall short of expectations and don't generate that guaranteed annual income, the government will step in and pay the suppliers the difference. Meanwhile, manufacturers of lower margin, non-patented molecules can make price increase requests to the reimbursement authority, which reduces the risk that manufacturers exit the market causing shortages. In context of this study, guaranteed annual income could potentially be provided if certain environmental requirements are met, such as discharge limits, protecting both the supply chain and the environment simultaneously.

***New Zealand – Improving supply chain transparency***

The New Zealand Medicines Regulatory Agency's Medsafe initiative requires that all approved drugs publicly specify the API, DP and finished dosage form manufacturers, and the local site of product release [28]. By knowing the number of suppliers at each stage, the government can identify bottlenecks in the supply chain and try to mitigate disruption. Additionally, by making the information publicly available, the government has a better view on where potential sources of pollution might be, and this could increase pressure on companies to source more sustainably [29]. However, such data would have to be real-time or regularly updated for maximal impact.

## Recommendations

The construction of any environmental measures can thus take many forms, based on the menu of "what", "how" and "who" options. To ensure the risk to the antibiotic supply chain is minimised, any new regulation or guidelines should include the following six elements:

1. **Evidence-based discharge limits:** Acknowledging that there is not yet agreement as to what manufacturing discharge limits are appropriate to suitably reduce AMR risk, any measures should ensure that the basis of limit selection is scientifically robust. This could be done by seeking consensus on the most suitable, pragmatic and evidence-based antibiotic discharge limits and measuring spot from an independent scientific advisory group with broad representation, also drawing on input from industry.

2. **Clear, verifiable methods for measurement and monitoring:** Clear methods should be outlined to make measures readily accessible and unambiguous, including where concentrations need to be measured, how frequently sampling needs to occur and how the values should be monitored and reported. Again, scientific advice should be applied when selecting the desired approach.

3. **Cost-efficient processes to meet and monitor standards:** As well as being evidence-based, decision-makers should also ensure that discharge limits and monitoring requirements are achievable by industry, with suitable technology and infrastructure options available that are not prohibitively expensive or complex to implement. Ideally, guidelines should be made available on how to achieve the limits in a cost-effective manner.

4. **Ambitious yet achievable timeframes for implementation:** Decision makers should ensure that they set ambitious timelines for implementation of any new approach, so momentum is maintained. However, industry must be engaged in the process to guarantee that timeframes are realisable and companies have sufficient time to invest in and implement any new waste treatment processes. Companies should have enough time to put in place protocols to monitor and audit their adherence to measures, both in-house and at third party suppliers (if required).

5. **Tiered approach:** Policy makers should consider how the measures could be tiered or tailored based on the fragility of the supply chain, aiming to mitigate negative impacts on supply in the supply chains that are at heightened risk of disruption, particularly for critical antibiotics that have few or no alternatives. This might be complemented by introducing supporting measures, such as adjusting timing for implementation in certain supply chains or introducing financial incentives for particularly at-risk supply chains.

6. **Internationally regulated or coordinated:** Given the global nature of the antibiotic supply chain and the antibiotic market, the most balanced approach to environmental measures would be internationally coordinated. This would help achieve maximum reach and impact of measures, but also avoid placing burden for change solely on countries where manufacturing happens by promoting supporting actions that can be taken by countries who are net importers, and mitigate impacts on LMICs who would be disproportionately affected by any supply chain disruption.

## Possible paths to action for implementing AMR-driven international environmental regulation

Considering the menu of "what", "how" and "who" options, and the six key recommendations made for reducing risk in the antibiotic supply chain, three possible paths to action for implementing AMR-driven environmental measures in manufacturing are further explored.

These focus on the importance of internationally coordinated options and will certainly require significant implementation time. Given each will come with its own complexities – whether diplomacy, capability or capacity-driven – there is merit in the named actors starting to examine feasibility in parallel to generate more evidence for which type of track may be most appropriate.

1. **Antibiotic discharge limits included in WHO GMP guidelines and implemented via national health regulators:** This would see leadership from WHO in bringing together consensus on appropriate standards, working with technical experts as well as member countries and wider stakeholders. This approach would likely have a high impact on reducing antibiotic discharge from manufacturing as over 100 countries have incorporated the WHO GMP provisions into their national laws, and sales would not be possible in these countries if the suppliers are not adhering to GMP guidelines.

   However, there is a potential increased risk of supply chain disruption for certain molecules because of the incremental running costs suppliers will have to incur, depending on the stringency of the guidelines. Hence, it would be important to ensure that standards are well thought out and appropriate supporting measures are put in place for the more fragile supply chains.

   The extensive coordination required across the WHO countries would also pose an implementation challenge. Moreover, GMP focusses on quality of medicine as opposed to the environment, therefore health inspectors might not currently possess the capabilities and expertise to perform audits or check suppliers for environmental non-compliance. It is also likely that more inspectors and resources will be needed. This would have to be considered carefully as monitoring frameworks are established.

2. **G20 environmental agreement implemented through national environmental regulation:** This would require a coordinated effort across G20 countries to include discharge limits in national environmental legislation, with compliance monitored by national environmental agencies (e.g. EPA in the US).

   This is expected to have a high impact on reducing antibiotic contamination as a high proportion of manufacturing sites are based in G20 countries. Again, depending on the stringency of the guidelines this approach might pose a potential additional risk of supply chain disruption for certain molecules and hence would require time for appropriate consultation, coordination and implmentation.

   The coordination required between G20 countries to achieve the highest impact and the coordination between national environmental and health ministries required could delay agreement and implementation.

3. **G7/G20 sustainable procurement implemented through national/local procurement agencies:** This would require a G7 or G20 coordinated effort for procurement agencies and organisations to include agreed discharge standards in procurement selection criteria. This mechanism could also allow rich countries to take a higher share of the burden, particularly if the procurement incentives are mainly driven by G7 countries.

   As this approach is based on a reward rather than a punitive selection, vulnerable supply chains unable to adapt to the measures will not be excluded from the tendering process, resulting in a lower risk of disruptions. However, in such supply chains, antibiotic contamination may still exist, and hence this approach is likely to have a more limited impact on antibiotic discharge from manufacturing (at least on lower volume and more fragile supply chains).

4. Challenges may also be faced in implementation because of the lack of centralised procurement for secondary care and particularly primary care in many countries. This may see varied requirements across countries for how they can best accommodate measures.

# APPENDIX

## Representative sample of antibiotics for analysis

A shortlist of 40 antibiotics representing the wide variety of different pharmacological properties, margins, resistance levels, formulations and manufacturing techniques found in the antibiotics business were selected (see Table 2).

These 40 shortlisted molecules represent 16 antibiotic classes including Aminoglycoside; Beta-lactams; Macrolide; Oxazolidinone; Glycopeptide; Lincomycin; Quinolone; Sulfonamide; Tetracycline; Polymyxin; and others as well as generic and patented molecules, various administration routes (oral, intravenous, inhalation and topical) and manufacturing techniques (fermentation, semi-synthetic and synthetic).

The prioritised list includes molecules with different risks to antimicrobial resistance as classified by the WHO AWaRe classification [25].

**Table 2** | Shortlist of 40 antibiotics used for supply chain mapping (I/II)

| Patented molecules | | |
|---|---|---|
| **Antibiotic classification** | **API** | **AWaRe Classification** |
| Aminoglycoside | Amikacin | A |
| Beta-lactam (Cephalosporin & beta-lactamase inhibitor) | Ceftolozane Sulfate; Tazobactam Sodium | R |
| Beta-lactam (Cephalosporin) | Ceftaroline Fosamil | R |
| Beta-lactam (Monobactam) | Aztreonam Lysine | R |
| Macrolide | Fidaxomicin | |
| Oxazolidinone | Tedizolid Phosphate | R |

**Legend**

WHO AWaRe Classification — A Access — W Watch — R Reserve

**Source:** Evaluate; WHO; expert interviews

## **Table 2** | Shortlist of 40 antibiotics used for supply chain mapping (II/II)

| Off-patent molecules | | |
|---|---|---|
| **Antibiotic classification** | **API** | **AWaRe Classification** |
| Aminoglycoside | Tobramycin | W |
| | Gentamicin | A |
| Beta-lactam (Carbapenem) | Cilastatin Sodium; Imipenem | W |
| | Ertapenem Sodium | W |
| | Meropenem | W |
| Beta-lactam (Cephalosporin & beta-lactamase inhibitor) | Avibactam; Ceftazidime | R |
| | Cefoperazone Sodium; Sulbactam Sodium | |
| Beta-lactam (Cephalosporin) | Ceftazidime | W |
| | Ceftriaxone Sodium | W |
| | Cefuroxime | W |
| | Cefalexin | A |
| Beta-lactam (Penicillin & Beta-Lactamase Inhibitor) | Amoxicillin; Clavulanic acid | A |
| | Piperacillin Sodium; Tazobactam Sodium | W |
| Beta-lactam (Penicillin) | Ampicillin | A |
| | Flucloxacillin | A |
| Glycopeptide | Vancomycin | W |
| Lincosamide | Clindamycin | A |
| Macrolide | Azithromycin | W |
| | Clarithromycin | W |
| | Erythromycin | W |
| Lipopeptide | Daptomycin | R |
| Quinolone | Ciprofloxacin | W |
| | Levofloxacin | W |
| | Moxifloxacin Hydrochloride | W |
| | Ofloxacin | W |
| Tetracycline | Tigecycline | R |
| | Doxycycline | A |
| | Minocycline | R *IV*<br>W *Oral* |
| Sulfonamide | Sulfamethoxazole And Trimethoprim | A |
| Polymyxin | Colistin (Polymyxin E) | R |
| Other | Trimethoprim | A |
| | Metronidazole | A |
| | Nitrofurantoin | A |
| | Linezolid | R |

**Legend**

WHO AWaRe Classification — A Access — W Watch — R Reserve

**Source:** Evaluate; WHO; expert interviews

# Methodology

### Mapping the trade flows of antibiotics

The flow of API volumes between countries was determined using UN Comtrade data, taking the import data for HS-4 code 2941 and HS-6 codes 300310, 300320, 300410, 300420.

### Mapping API manufacturing sites of 40 shortlisted antibiotics

Data from Cortellis (Clarivate) was used to determine manufacturers' ability to produce the shortlisted APIs, and the site location (country and city). This data represents manufacturing sites that are or were able to manufacture and not necessarily those that are currently able to or actively manufacturing. Hence, the Cortellis data was validated by carrying out further research to determine whether these sites are still able to or actively making the molecule, including via some direct manufacturers reach outs.

The Cortellis database under-represented Chinese manufacturing sites, therefore further research was carried out to identify any additional sites in China that manufactured the 40 shortlisted APIs.

### Determining the economic impact of new regulations

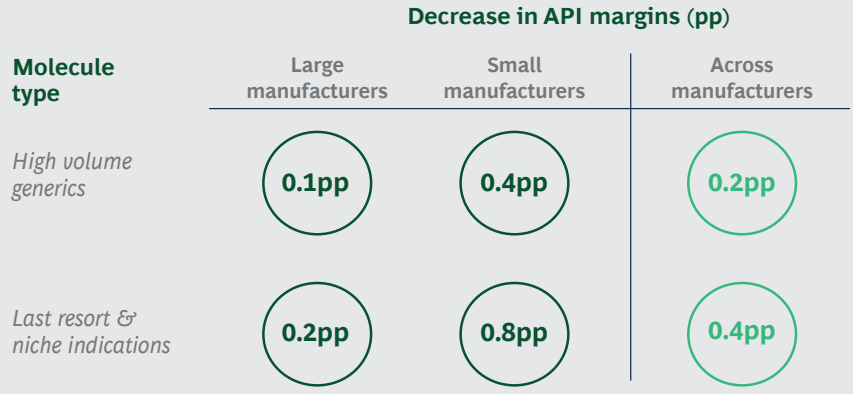
The economic impact of adhering to new regulations was determined through expert interviews with manufacturers, industry groups and civil society, and supplemented with further research into wastewater treatment processes and monitoring equipment costs. Moreover, the economic impact of new regulations was determined separately for API and DP manufacturers:

*Economic impact on API manufacturers:*

To determine the economic impact of new regulations, incremental running costs were estimated, which include depreciated capital investment, labour and utilities, for both wastewater treatment and monitoring, differentiating between small and large manufacturers in Options A and B. Small manufacturers will require greater investments in both Options A and B as their current wastewater treatment infrastructure will likely be less advanced when compared to large manufacturers. In Option A, 0.5% incremental running costs were estimated for large manufacturers and 2% for small manufacturers. In Option B, 5% incremental running costs were estimated for large suppliers and 10% for small suppliers.

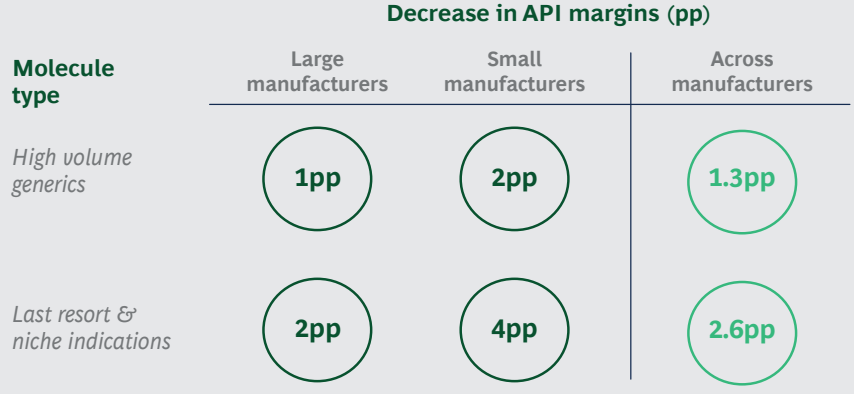
Next, the impact of these incremental running costs on profitability was determined by estimating the margin decrease they would lead to. First, the percentage of total costs that are running costs per type of molecule was estimated. For high volume generics, running costs were estimated at 20% of total costs, whereas for antibiotics with niche indications and last resort generics, that are often produced at lower volumes, running costs were estimated at 40% of total costs (the remainder of the cost is raw materials). Secondly, the percentage decrease in API margin per type of molecule was calculated by multiplying the incremental cost increase determined previously by the percentage running cost over total cost (20% vs. 40%) for both Option A and B. Assuming manufacturers would absorb all the costs, this led to a decrease in API margins as illustrated in Figure 9 and Figure 10 for Option A and B respectively.

**FIGURE 9 |** Decrease in API margins by molecule type and size of manufacturer in Option A, assuming API manufacturers would absorb all the costs




**Source:** Expert interviews; BCG analysis

**FIGURE 10 |** Decrease in API margins by molecule type and size of manufacturer in Option B, assuming API manufacturers would absorb all the costs




**Source:** Expert interviews; BCG analysis

Finally, the weighted average of the decrease in API margins was calculated assuming a split of large to small manufacturers of 70% to 30%. Assuming manufacturers would absorb all the costs, this led to a decrease in API margins of 0.2pp for high volume generic and 0.4pp for last resort generics and antibiotics with niche indications in Option A, and 1.3pp for high volume generics and 2.6pp for last resort generics and antibiotics with niche indications in Option B. Using market data, the market share per type of molecule was estimated: 57% for high volume generics, 38% for last resort generics and antibiotics with niche indications, and 4% for patented molecules. This led to a ~0.3pp average decrease in margins in Option A and a ~1.8pp average decrease in Option B.

*Economic impact on DP manufacturers:*

The same methodology was applied do determine the economic impact of new regulations on DP manufacturers, but the same investment for large and small manufacturers was assumed as expert interviews indicated limited differences. In Option A, incremental running costs were estimated at 3.5%, while in Option B, incremental running costs were estimated at 6%. Note that the incremental running cost in Option A (3.5%) is higher compared to API manufacturers (0.5-2%) as research indicated that API manufacturers are often more advanced compared to DP manufacturers on wastewater treatment and monitoring.

Next, the impact of these incremental running costs on the DP profit pool was calculated by estimating the margin decrease they would lead to. The same estimates were used for the percentage of total costs that are running costs per type of molecule as for API manufacturers (high volume generics running costs are 20% of total costs, antibiotics with niche indications and last resort generics running costs are 40% of total costs). The percentage decrease in DP margin per type of molecule was calculated by multiplying the incremental cost increase determined previously by the percentage running cost over total cost (20% vs. 40%) in Options A and B. Assuming manufacturers would absorb all the costs, this led to a decrease in DP margins of 0.7pp for high volume generic and 1.4pp for last resort generics and antibiotics with niche indications in Option A, and 1.2pp for high volume generics and 2.4pp for last resort generics and antibiotics with niche indications in Option B.

*Total economic impact:*

The current antibiotic market had an estimated total value of ~$44 billion in 2020 [18]. Cost of goods sold (COGS) are estimated to be 40-50% of the revenue in this market highly penetrated by generics. Therefore, the API market size was estimated to be ~$8B and the DP market to be ~$6B, with a $1B and $1.1B profit pool respectively. That brings total profits for the DP and API stages to ~$2.1 billion per annum.

Using the previously described calculations it is estimated that running costs (all costs excluding raw materials) are $1.9B for API manufactures and $1.4B for DP manufacturers bringing the total across both stages to $3.3B. Similarly from previously described calculations it is estimated that Option A would add 2% ($80M) to the running cost base in Option A and 7% ($250M) in Option B across API and DP manufacturers.

When estimating the financial impact of regulations and who will absorb these additional costs, two extreme scenarios exist. The first scenario assumes that all costs are absorbed by the API and DP manufacturers, while the other assumes all costs are transferred to the market, pushing up market prices.

If all costs were to be absorbed by the API and DP manufacturers Option A would lead to an estimated 4% ($80M) profit decrease, and Option B a 12% ($250) decrease.

On the other hand, if all cost increases of $80M in Option A and $250M in Option B were transferred to the $44B antibiotics market, it would lead to a limited average price increase of <1% in both options (see Figure 8).

### Deaveraging risk under Option B

As outlined previously, the molecules in the "additional risk under Option B" zone of the margin/supply matrix were assessed across five parameters: number of manufacturing sites, manufacturer size, manufacturer portfolios, API margins and the geographical concentration of manufacturing sites. The thresholds used to classify each molecule as red, amber or green (green being most resilient, red being highest risk) are shown in Figure 11.

**FIGURE 11 |** RAG rating thresholds for the five parameters

| | Metrics for determining risk | Red | Amber | Green |
|---|---|---|---|---|
| 1 | **No. sites producing** \| *Few sites means high risk of disruption when 1 manufacturer ceases to produce* | ≤4 | 5-6 | >6 |
| 2 | **Size of players** \| *Small manufacturers less able to absorb additional costs* | ≥60% | 30-60% | ≤30% |
| 3 | **Geographical concentration** \| *Geographically concentrated sites increase susceptibility to disruption* | ≥60% | 30-50% | ≤30% |
| 4 | **Proportion of API portfolio in antibiotics** *If only small % of portfolio in antibiotics, new investment not worthwhile and players likely to switch* | ≥60% | 30-60% | ≤30% |
| 5 | **Margins** \| *Decrease in already thin margins may cause manufacturers to exit* | ≤10% | 10-15% | ≥15% |

**Source:** Expert interviews; BCG analysis

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