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**- English translation -**

# Precarious antibiotics supply situation: Will the Covid19 Pandemic change anything?

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From the outset, the COVID-19 pandemic has drawn broader public attention to the dependence on global pharmaceutical supply chains. Relatively early on, the world's leading producer of generics – India - imposed export restrictions, including for certain antibiotics[2]. One concern was that such measures, coupled with spikes in demand for certain medicines, could lead to dramatic supply shortages. Several countries did indeed experience such shortages, including for propofol and other anaesthetics, hydroxychloroquine, later dexamethasone and, in particular, different medical products such as masks, respirators and oxygen.

## Where do we stand?

Supply shortages were already a major issue before COVID-19. The therapeutic products platform of the Swiss Federal Office for National Economic Supply reported a total of 238 interruptions in the supply of medicines for the 2019 reporting year, representing an increase in 90 % by comparison to the preceding year.[3] The platform was created pursuant to the Ordinance on the Essential Human Medicines Reporting Office (SR 531.215.32), which establishes an obligation for marketing authorization holders to report current or projected interruptions in the supply or delivery of a given dose or form expected to last for more than a fortnight[4]. While the Reporting Office only captures essential medicines for national supply listed in the annex of the above-mentioned ordinance, www.drugshortage.ch reports on

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[2] Vindu Goel. As Coronavirus Disrupts Factories, India Curbs Exports of Key Drugs. New York Times. 6 March 2020. https://www.nytimes.com/2020/03/03/business/coronavirus-india-drugs.html.

[3] Federal Office for National Economic Supply, Essential Human Medicines Reporting Office, Report 2019.

[4] For details, see: Mühlebach, S., Haudenschild, U. Schäublin, M. Versorgungsstörungen bei wichtigen Arzneimitteln (Supply disruption in essential medicines), Pharm. Ind. 80, No. 5 (2018), pp. 594-601.

shortages in the supply of all products covered by health insurances and products otherwise relevant to hospitals. Supply shortages reported by users on this site have more than doubled between 2016 and 2019.

According to the French National Agency for the Safety of Medicines and Health Products (ANSM), the number of reported supply disruptions in France increased nearly twentyfold between 2008 and 2018.[5] In the United States of America, delivery disruptions have increased again recently after a temporary peak in 2011.[6]

While supply disruptions can also occur in higher-priced patented products, for example if there are production-related problems, they are more frequent in older products characterized by complex production processes (parenteral formulations) and low profit margins resulting from low prices or small volumes[7]. This is the case for the supply of antibiotics, most of which are older than average while at comparatively low price. Accordingly, the situation regarding antibiotics supply in Switzerland continued to deteriorate in 2019: there were 53 supply disruptions for systemic antibiotics, 32 of which concerned parenteral formulations, affecting 20 different active ingredients and combinations thereof.[8] A survey conducted by the European Association of Hospital Pharmacies (EAHP) revealed that antimicrobial drugs are particularly vulnerable to supply disruptions.[9] Anti-infectives for systemic use are the most affected group of drugs in Switzerland,[10] and the third most affected group in France.[11]

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[5] Ministère des Solidarités et de la Santé, « Lutter contre les pénuries et améliorer la disponibilité des médicaments en France. Feuille de route 2019-2022 » (Ministry for Solidarity and Health, "Addressing shortages and enhancing the availability of medicines in France. 2019-2022 Road Map"). https://solidarites-sante.gouv.fr/IMG/pdf/31142_dicom_pe_nurie_de_me_dicamentsv8.pdf; https://www.vie-publique.fr/sites/default/files/rapport/pdf/274702.pdf

[6] Federal Drug Administration, Drug Shortages and Root Causes and Potential Solutions, 2019.

[7] Federal Drug Administration, Drug Shortages and Root Causes and Potential Solutions, 2019; for National Economic Supply FONES, Essential Human Medicines Reporting Office, Report 2019.

[8] Federal Office for National Economic Supply FONES, Essential Human Medicines Reporting Office, Report 2019.

[9] EAHP. Survey on Medicines Shortages to improve patient outcomes (2018) https://www.eahp.eu/sites/default/files/report_medicines_shortages2018.pdf.

[10] Federal Office for National Economic Supply FONES, Essential Human Medicines Reporting Office, Report 2019.

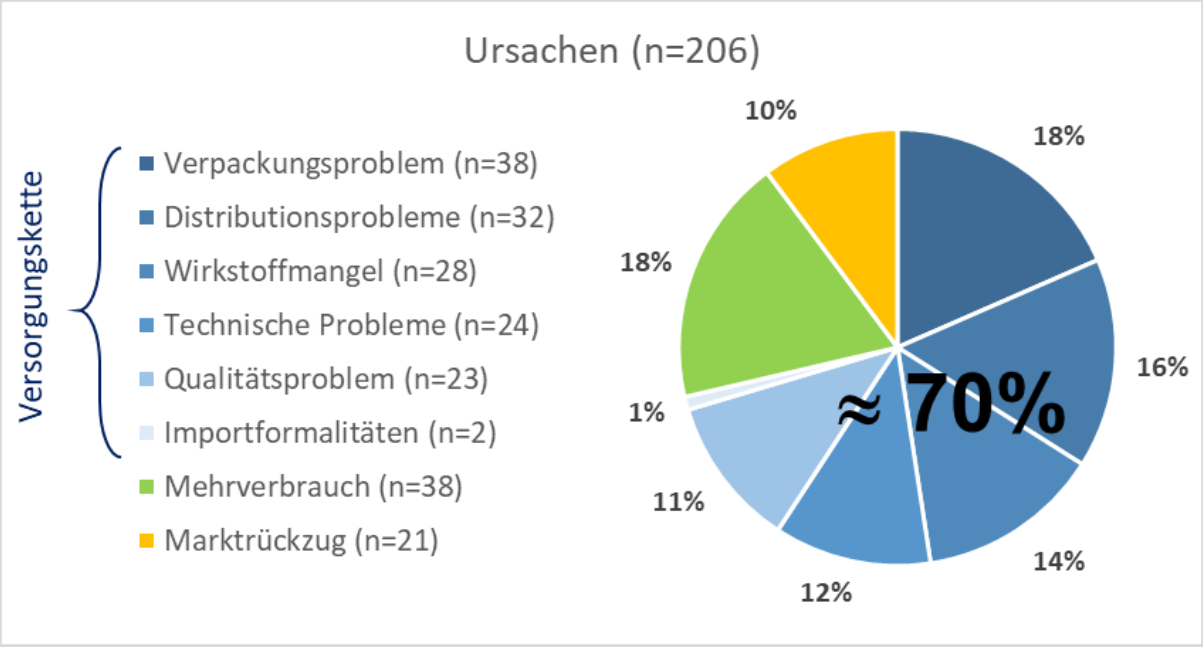
[11] Agence nationale de sécurité du médicament et des produits de santé, « Risque de rupture de stock et ruptures de stock des médicaments d'intérêt majeur. » (French National Agency for the Safety of Medicines and Health Products, "Risk of shortages and shortages of drugs of major interest". https://www.ansm.sante.fr/S-informer/Informations-de-securite-Ruptures-de-stock-des-medicaments/Risque-de-rupture-de-stock-et-ruptures-de-stock-des-medicaments-d-interet-majeur

**What are the main reasons for supply disruptions in Europe?**
While the reasons for supply disruptions can be categorized or presented in different ways, the common denominator is their interconnectedness and the fact that economic aspects have a major impact on other factors, especially on the supply side.

| Economic reasons | Supply-side reasons | Demand-side reasons | Product-specific reasons | Regulatory reasons |
|---|---|---|---|---|
| Market withdrawal | Shortage of suppliers | Surging demand (shortfall of other products, pandemic, new treatment guidelines, emerging markets) | Low volume | Factory closures (on environmental grounds) |
| Closure of individual factories | Supply-chain issues (quality issues, accidents) | Poor procurement planning | Complex production process (IV products) | Stronger regulatory requirements |
| | Low stocks | Single supplier dependence | Few alternative products with equivalent effect | Export bans |

Table 1: Main reasons for supply disruptions in Europe by category. In many less developed health systems, there may be numerous other reasons.

In Switzerland, about 70 % of supply disruptions can be traced back to supply chain issues and 11 % to market withdrawal.



**Causes (n=206)**

Supply chain:

- Packaging issues (n=38)
- Distribution issues (n=32)
- Shortage of active ingredient (n=28)
- Technical problems (n=24)
- Quality issues (n=23)
- Import formalities (n=2)
- Increased consumption (n=38)
- Market withdrawal (n=21)

Diagram 1: Causes of supply disruptions
Source: Federal Office for National Economic Supply, Essential Human Medicine Reporting Office, Report 2019.

This is associated with increasing supply chain complexity in the pharmaceutical industry. Often, each production stage reflected in diagram 2 is carried out in a different plant and potentially in a different country. Traditionally, China is a key location for the potentially highly pollutant raw ingredient production, while the Indian industry has specialized mostly in the manufacturing of active ingredients and subsequent production stages. Both production stages traditionally work with smaller profit margins at high volume. In recent years, active ingredient production had increasingly shifted to China, which is currently the world's leading producer of active ingredients with an estimated market share of 40 %.[12] India, the world's largest manufacturer of generics, sources 70 % of active ingredients from China.[13]

[12] OptimaInsights, China, API Market By Drug Type and Forecast 2026, February 2019, https://www.optimainsights.org/reports/69-china-api-market; in 2009, the World Bank estimated its market share only at 20 %: Janet Bumpas & Ekkehard Betsch, "Exploratory Study on Active Pharmaceutical Ingredient Manufacturing for Essential Medicines", World Bank Health, Nutrition and Population (HNP) Discussion Paper. September 2009.
[13] Chatterjee P. "Indian pharma threatened by COVID-19 shutdowns in China", in The Lancet, vol. 395, No. 10225, p. 675 (2000).

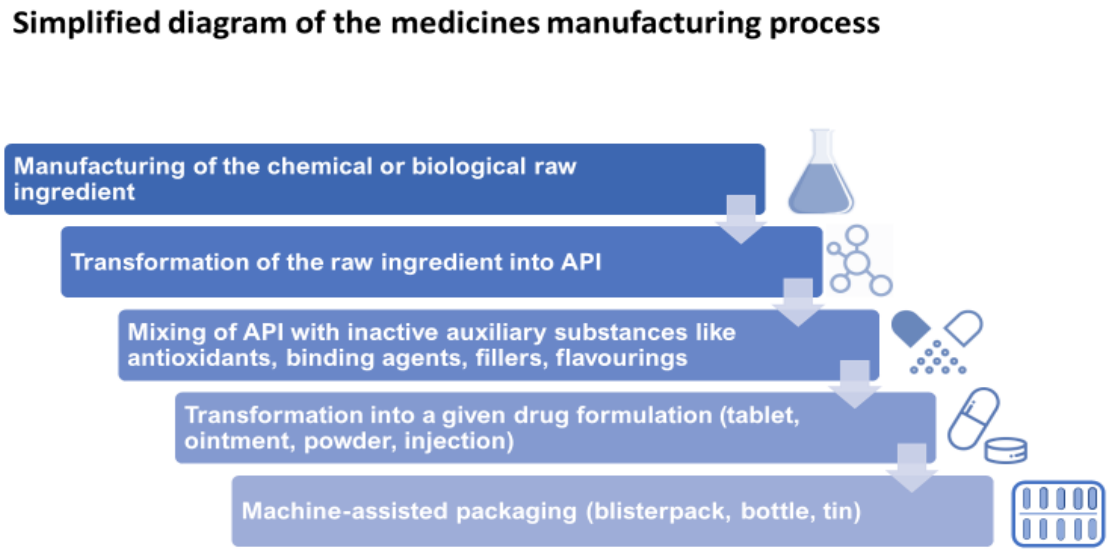



Diagram 2: Simplified diagram of medicines production

Especially with lower-priced products, margin pressure leads to cost optimization at the production stage – such as switching from in-house production to external suppliers of active ingredients – and supply-chain and inventory optimization, which can lead to supply disruptions. The last resort is complete market withdrawal. The explanation provided by GlaxoSmithKline (GSK) in June 2020 for its decision to close down its penicillin production in the United Kingdom is symptomatic in this regard:

"Following a global review of antibiotics production by GSK, we concluded that the sterile production of amoxicillin in a highly competitive environment is no longer viable. We have therefore decided to phase out production in Europe. In Switzerland, this affects the parenteral antibiotic clamoxyl. We therefore wish to inform you in good time that clamoxyl will no longer be commercialized in Switzerland."[14]

Thus, Sandoz, with its facility in Kundl, Austria, is the last major vertically integrated manufacturer of penicillin/amoxillin in Europe. Only a multi-million subsidy from the Austrian Government in 2020 could prevent Sandoz from discontinuing these long-standing operations. Sandoz already sold a manufacturing facility for active ingredients of cephalosporine in Frankfurt, Germany, in 2015.[15] The reasons were, again, fierce pressure on margins in a global market where active ingredients can be sourced at much lower cost,

[14]https://www.bwl.admin.ch/dam/bwl/de/dokumente/themen/heilmittel/meldestelle/update_vertrieb_clamoxyl.pdf

[15] Michael McCoy, "Sandoz to shore up Europe's last antibiotics plant. Company and Austrian government will invest to ensure local antibiotic production", Chemical and Engineering News, vol. 98, issue 30, 30 July 2020.

especially from China. This is due to cheaper labour and production costs, among others, but also to lower environmental standards for chemical manufacturing processes.[16]

Market withdrawal of antibiotics are not the exception: approximately 11 % of supply disruptions reported to the therapeutic products platform in Switzerland result from market withdrawals (21 reports, mostly parenteral products); 62 % of these market withdrawals concerned antibiotics (7 for co-amoxillin, 3 for ciprofloxacin, 2 for piperacillin/tazobactam and 1 for norfloxacin). Switzerland is thus left with a single supplier of parenteral co-amoxillin, which causes supply disruptions that cannot be fully compensated by compulsory stockpiling. Only five out of 13 active ingredients used in oral antibiotic formulations for children in Switzerland can be obtained from more than one supplier. [17] In Germany in 2015 there was a single supplier for a total of 23 active ingredients of antibiotics.[18]

**The example of Benzylpenicillin**

Benzylpenicillin, which is essential in the treatment of syphilis, is a good example of global trends. Since the beginning of the millennium, six manufacturers of active ingredients and more than 40 end-product manufacturers have withdrawn from the market, leaving only four active ingredients manufacturers worldwide. The frequent supply disruptions are attributed to three main reasons:

(1) Many countries source benzylpenicillin from a wholesaler, which obtains the product from an end-product manufacturer which, in turn, procures the active ingredient from an API manufacturer. As a result, there are no alternatives in the event of supply chain-related problems.

(2) In most countries, benzylpenicillin costs only a few cents per dose, but its production as a sterile injectable is complex and relatively expensive. Consequently, a growing number of producers withdraw.

(3) Inaccurate demand forecasts, weak procurement systems and knowledge gaps in the treatment of syphilis. [19]

[16] Janet Bumpas & Ekkehard Betsch, "Exploratory Study on Active Pharmaceutical Ingredient Manufacturing for Essential Medicines", World Bank Health, Nutrition and Population (HNP) Discussion Paper, Sept. 2009.

[17] Federal Office for National Economic Supply FONES, Essential Human Medicines Reporting Office, Report 2019.

[18] IGES Institut, „Versorgungsrelevanz generischer Antibiotika – Marktentwicklung, Regulierung und Versorgungssicherheit" ("Supply-relevance of generic antibiotics – market trends, regulation and supply security") , January 2017.

[19] Nurse-Findlay S, Taylor MM, Savage M, Mello MB, Saliyou S, Lavayen M, Seghers F, Campbell ML, Bigirimana F, Ouedraogo L, Pyne-Mercier L , Supply, Demand, and Shortages of Benzathine Penicillin for Treatment of Syphilis: A Market Assessment. PLoS Med. 2017; 14(12): e1002473.

As a general rule, the fewer the suppliers, the greater the risk of supply disruption. The number of suppliers of a given drug can be misleading: in 2017, an explosion at a manufacturing facility for the active ingredient of the antibiotic piperacillin in China resulted in global supply disruption for piperacillin (and the piperacillin/tazobactam combination) although there are several marketing authorization holders.[20] The accident showed that all these companies had sourced the active ingredient from the same Chinese manufacturer. Only the company itself and the regulatory authority – Swissmedic for Switzerland – know where marketing authorization holders purchase active ingredients. The extent of dependence on certain big API manufacturers is therefore hard to gauge. In the context of a WHO project, it was estimated that more than 50 % of marketing authorization holders of 10 selected antibiotics that had been subject to repeated supply disruptions source the API from only two manufacturers.[21] Since API origin and supply chains are confidential, it is very difficult to identify those products whose particularly strong dependence on few manufacturers places countries' supply security at risk.

**The role of the regulatory environment**

Each supply chain modification, such as production relocation following factory closure or a change of API supplier, must be reported to the regulatory authority in the country or region where the product is marketed and licensed. As a result of such regulatory requirements, global companies must plan any change in API supplier years in advance to allow for alignment of national marketing authorizations. Tougher regulatory requirements for more complex products in qualitative terms – such as injections – also affect production costs.

**Why do market laws of supply and demand not resolve the problem?**

In a normal market environment, high pressure on prices combined with competition would create a situation where only one or few suppliers survive, followed by price increases which, according to market laws, would attract new suppliers. While such extreme price increases have occurred where old generics have a monopoly status, as with Daraprim[22], notably in the United States, it is uncertain whether this brings new suppliers to the market. The initial investment in the production of a drug product is very high. Moreover, new marketing authorizations must be obtained for each country in order to enter a highly price-regulated market which is rather unattractive when compared with newer generics or biosimilars. Market entry of new generics suppliers with old products is therefore rare, even

[20] Judy Stone. Fragile Antibiotic Supply Chain Causes Shortages And Is A National Security Threat. Forbes. 1 June 2018. https://www.forbes.com/sites/judystone/2018/06/01/fragile-antibiotic-supply-chain-causes-shortages-and-is-a-national-security-threat/#18840078adf3

[21] WHO, Meeting report: antibiotic shortages: magnitude, causes and possible solutions, 2019. https://www.who.int/publications/i/item/meeting-report-antibiotic-shortages-magnitude-causes-and-possible-solutions

[22] Andrew Pollack. Drug Goes From $13.50 a Tablet to $750, Overnight. New York Times Sept. 20, 2015. https://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html

if only one or few suppliers remain on the market, especially for small markets or niche products.[23]

**What action have countries taken in recent years?**

Many countries like the United States, France, Switzerland and Germany have created voluntary public registers[24] or require companies to notify supply disruptions in advance wherever possible. Switzerland has created compulsory stockpiles, which are financed by the industry and can be used in the event of supply disruption. Germany has authorized the importation of not licenced drugs in the event of supply problems. Similar measures are in place in many European countries. However, most of these measures do not seek to address the causes of increasing supply disruption, but instead to manage and absorb such disruptions. These measures have been tried and tested in Switzerland and, as shown in the report of the Swiss Federal Office for National Economic Supply, have enabled early recognition and bridging of supply bottlenecks. The therapeutic products platform and the analysis conducted by the Swiss Federal Office for National Economic Supply help identify the main reasons for supply disruption and particularly at-risk products. They also make it possible to quantify the extent of the problem, which is crucial for the development of long-term solutions. Bearing in mind the abovementioned facts and given the large number of market withdrawals, the problem is likely to grow, rather than dissipate, in future.

**Innovative approaches**

COVID-19 has made politicians in the United States and Europe aware of the heavy dependence of the pharmaceutical sector. In the United States, BARDA[25] granted US$ 354 million to the pharmaceutical company Phlow in Mai 2020, with an optional US$ 812 million over 10 years, instructing the company to manufacture essential medicines in the United States. Phlow is a recently established drug manufacturer that describes itself as a “A public benefit corporation dedicated to manufacturing and securing our nation's most essential medicines, 100% in the U.S” and commits to transparent pricing.[26]

Phlow is associated with Civica Rx, a non-profit drug manufacturer founded in 2018 by seven private American health providers to source and manufacture generics affected by chronic supply shortages and excessive pricing. Civica Rx currently serves more than 1 200 hospitals, representing 30 % of all hospital beds in the United States.[27] Civica Rx pursues a strategy involving in-house production of essential drugs, on the one hand, and the conclusion of long-term supply agreements based on predictable volumes and transparent pricing with

[23] FDA 2019.
[24] For a list of national registers of European Union Member States, see: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/availability-medicines/shortages-catalogue
[25] Biomedical Advanced Research and Development Authority des U.S. Department of Health and Human Services
[26] https://www.phlow-usa.com/
[27] https://mk0sakunexoeoby9gsa0.kinstacdn.com/wp-content/uploads/2020/09/Civica-Two-Years_FINAL-3.pdf

vertically integrated manufacturers, on the other, thus ensuring supply security. To this end, Civica Rx concluded its first agreement for the manufacturing of vancomycin and daptomycin with Xellia Pharmaceuticals in May 2019. Xellia produces active ingredients and sterile injectable drugs in-house.[28] In July 2020, Civica Rx and Sandoz announced the conclusion of a five-year agreement for the manufacturing and supply of six parenteral drug products (antibiotics, antihypertensives, blood thinners and acid-reducing agents).[29]

In France, President Macron announced a drug manufacturing repatriation policy in June 2020, which provides for a 120 million euros investment in new production lines for 100 % locally produced paracetamol, which has been difficult to source during the pandemic.[30]

In Germany, the coalition Government has decided that the country should expand capacities and gain greater independence, including in the production of therapeutic substances and intermediates, and set aside 1 billion euros for this purpose.[31]

As mentioned above, Austria has recently provided a subsidy to Sandoz in order to secure penicillin manufacturing at the Kundl site for the next decade.

In Switzerland, discussions are under way on the possibility to entrust the manufacturing of certain medicines to the military pharmacy, which holds a Swissmedic manufacturing licence. However, both the military pharmacy and university hospital pharmacies would have to rely on external suppliers of active ingredients.

Austrian-style manufacturing subsidies can be useful where they prevent impending closure of production. In the long run, subsidies would however accelerate the downward trend in prices. If European manufacturing were subsidized to an extent that enabled companies to bid successfully alongside foreign manufacturers, competitors are likely to cut prices even further to make optimal use of their existing production capacities. As a result, margin pressure continues to rise, more unsubsidized manufacturers withdraw and subsidies must eventually be increased to remain competitive. Ultimately, the State would subsidize artificially low purchasing prices.

Antibiotic drug manufacturing by private companies in Europe is only sustainable over time if products are competitive. However, as shown in a study conducted by Roland Berger on behalf of Pro Generika on cephalorosporin manufacturing in Germany, they cannot compete

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[28] https://civicarx.org/civica-rx-and-xellia-pharmaceuticals-join-forces/

[29] https://civicarx.org/sandoz-collaborates-with-civica-rx-to-help-reduce-critical-generic-medicine-shortages-in-us-hospitals/

[30] https://www.lemonde.fr/economie/article/2020/06/18/le-gouvernement-amorce-une-politique-de-relocalisation-des-medicaments_6043337_3234.html

[31] Bundesregierung, Corona-Folgen bekämpfen, Wohlstand sichern, Zukunftsfähigkeit stärken, Ergebnis Koalitionsausschuss 3. Juni 2020, Berlin 2020 (The German Federal Government, „Tackling the impact of corona, ensuring prosperity, strengthening sustainability", outcome coalition committee, 3 June 2020, Berlin 2020). https://www.bmwi.de/Redaktion/DE/Downloads/E/eckpunktepapier-corona-folgen-bekaempfen.pdf?__blob=publicationFile&v=6

in price. [32] Simply increasing prices is no solution for a small market like Switzerland either; for lack of volume, it would have no real impact on decisions like that of GSK, nor would it necessarily enhance supply security.

A more long-term solution would be for buyers to pay extra for security of supply. Civica Rx is a good example. A more sustainable solution could be for European buyers to include supply security-related conditions systematically in calls for tender – within the limits of procurement law – and to evaluate tenders on that basis in addition to price, for example:[33]

- Awarding contracts systematically to two manufacturers, instead of ordering the total quantity from the cheapest supplier (difficult for small volumes and when there is only one remaining supplier).
- Requiring manufacturers to provide supply chain transparency
- Requiring manufacturers to include alternative scenarios in the event of supply chain problems in their proposal
- Requiring manufacturers to explain what makes their company is particularly resilient against supply disruptions (e.g. modern production facilities)
- Requiring manufacturers to source active ingredients from two manufacturers
- Guaranteeing compliance with high environmental standards throughout the supply chain
- Rewarding short supply chains when evaluating tenders

It would be important for buyers to avoid setting different standards, as this would generate additional costs. A label or an international norm like the one proposed by the American Federal Drug Authority[34] could be one option. For Switzerland, a privately managed model such as Civica Rx could also be worth exploring, bearing in mind the market size (30 % of hospital beds in the United States) probably makes it much easier for Civica Rx to conclude advantageous agreements.

Public tendering should reward companies that invest in resilient supply chains, supply security, environmental standards and local production. Price thereby loses relative importance in the selection process, which means that higher priced products become competitive to the extent that they score in other areas. If major buyers in Europe systematically set similar conditions of tender, it could potentially change the dynamic of the antibiotics market. It is therefore crucial to include buyers and manufacturers in discussions on sustainable solutions to supply shortages. Buyers, to convince them that more sustainable tendering practices will save them money in the long run, and manufacturers, to

[32] Roland Berger, Studie zur Versorgungssicherheit mit Antibiotika: Wege zur Produktion von Antibiotikawirkstoffen in Deutschland bzw. der EU, Ergebnisbericht, 2018 (Study on security of antibiotic supply: pathways to producing active ingredients of antibiotics in Germany or Europe. Outcome report, 2018).

[33] It might also be an option to penalize supply disruptions. This measure would nevertheless require for companies to invest with foresight to avoid payment of potential penalties. Whether this is the case is unclear, since sales are not necessarily fed back into investment decisions.

[34] Federal Drug Administration, “Drug Shortages and Root Causes and Potential Solutions”, 2019.

find out which options they see for making supply chains more resilient. The members of the AMR Industry Alliance have committed to compliance with certain environmental standards throughout the supply chain[35] and therefore have an interest in others complying with those standards well.

At the same time, regulators like Swissmedic should ensure supply chain transparency by disclosing at least the names of the active ingredient manufacturers. This is already standard in most other industries. Apple or Hennes & Mauritz, for example, disclose the names of all their suppliers.[36] In Germany and France, new laws on supply chain responsibility might also lead to greater transparency in the pharmaceutical sector.[37] Such transparency and environmental and human rights due diligence requirements for suppliers would also ensure that the same rules apply to all.

**Outlook**

Summing up, COVID-19 put a spotlight on the fragility of pharmaceutical supply chains and the growing dependence on few manufacturers. This has added considerable momentum to the discussion on sustainable solutions. Even prior to the pandemic, governments have taken a series of apparent actions, which attenuate the problem but fail to provide sustainable solutions. COVID-19 has moved countries into action mode, which could bring about short- or long-term subsidies or the establishment of parallel public supply capacities. Still, the most sustainable solutions would be those involving cross-border dialogue with market participants, buyers and manufacturing companies that facilitate the establishment of more sustainable economic structures in the long run.

[35] https://www.amrindustryalliance.org/shared-goals/common-antibiotic-manufacturing-framework/

[36] Apple. Supplier List. 2020. https://www.apple.com/supplier-responsibility/pdf/Apple-Supplier-List.pdf; H&M Group. Supplier List. 2020. https://hmgroup.com/sustainability/leading-the-change/supplier-list.html.

[37] The German Federal Government. National Action Plan Implementation of the UN Guiding Principles on Business and Human Rights 2016-2020. Berlin: Federal Foreign Office, 2017; Loi n°2017-399 relative au devoir de vigilance des sociétés mères et entreprises donneuses d'ordre, aussi dite « loi sur le devoir de vigilance » (Act No. 2017-399 on due diligence of parent companies and contracting companies, also known as "due diligence act").