Potential measures to facilitate the production of active pharmaceutical ingredients (APIs)
Abstract

European countries have been experiencing medicine shortages due to disruptions in the supply chain. Reshoring the production of active pharmaceutical ingredients (APIs) is considered an approach to secure the supply. This study informs about the current API production in the European Union, including reshoring initiatives. Studying potential benefits and challenges of local API production and the processes of reshoring, the document explores measures to facilitate the production of APIs in the European Union.

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This document was requested by the European Parliament’s Committee on the Environment, Public Health and Food Safety.

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## CONTENTS

**LIST OF BOXES**  
**LIST OF FIGURES**  
**LIST OF TABLES**  
**LIST OF ABBREVIATIONS**  
**EXECUTIVE SUMMARY**  
1. **BACKGROUND**  
2. **METHODS**  
   2.1. Aim and scope  
   2.2. Terminology  
   2.3. Literature search  
      2.3.1. Search for scientific publications and studies (systematic search)  
      2.3.2. Search for documents and grey literature (hand search)  
   2.4. Interviews  
3. **RESULTS**  
   3.1. Mapping of relevant documents  
      3.1.1. Key documents at EU level  
      3.1.2. Other relevant documents  
   3.2. Current situation of active pharmaceutical ingredient (API) production  
      3.2.1. Overview of API production in Europe  
      3.2.2. Existing incentives and measures to promote API production in Europe  
4. **CONCLUSIONS AND RECOMMENDATIONS**  
   4.1. Summary of findings and conclusions  
   4.2. Recommendations  
**REFERENCES**  
**ANNEX**  
   Search strategies  
   Detailed information from relevant documents
LIST OF BOXES
Box 1: Terminology regarding "reshoring" 12
Box 2: Terminology regarding "locality" 12

LIST OF FIGURES
Figure 1: Generic illustration of the pharmaceutical supply chain 10
Figure 2: Flow chart of document selection 14
Figure 3: Barriers to reshoring – results from a survey with companies 21
Figure 4: Distribution of API manufacturers (2019) 24
Figure 5: Certificates of Suitability of Monographs of the European Pharmacopoeia for APIs 25
Figure 6: API production sites per country (2022/2023) 26

LIST OF TABLES
Table 1: Dimensions of the scope of the in-depth analysis 11
Table 2: Overview of key documents at EU level 17
Table 3: Overview of documents from supranational organisations or at national level 19
Table 4: Overview of documents from industry and their associations 20
Table 5: Overview of other documents (mainly studies) 22
Table 6: Overview of government initiatives to promote API production in Europe 28
Table 7: Challenges of reshoring and their potential solutions 31
Table 8: Search strategy for systematic literature search 43
Table 9: Search terms and strings for hand search 44
Table 10: Documents at EU level 45
Table 11: Documents prepared by supranational organisations or at national level 48
Table 12: Documents from industry and their associations (excerpt) 52
Table 13: Other documents (mainly studies) 54
### LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>API</td>
<td>Active pharmaceutical ingredient</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical</td>
</tr>
<tr>
<td>CEP</td>
<td>Certificate of Suitability of Monographs of the European Pharmacopoeia</td>
</tr>
<tr>
<td>CM</td>
<td>Continuous manufacturing</td>
</tr>
<tr>
<td>EC</td>
<td>European Commission</td>
</tr>
<tr>
<td>EFPIA</td>
<td>European Federation of Pharmaceutical Industries and Associations</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>ENVI</td>
<td>Environment, Public Health and Food Safety</td>
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<tr>
<td>EPHA</td>
<td>European Public Health Alliance</td>
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<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>HERA</td>
<td>Health Emergency Preparedness and Response</td>
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<tr>
<td>IDA</td>
<td>In-depth analysis</td>
</tr>
<tr>
<td>KSM</td>
<td>Key starting material</td>
</tr>
<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
</tr>
<tr>
<td>PAT</td>
<td>Process analytical technology</td>
</tr>
<tr>
<td>TSI</td>
<td>Technical Support Implementation</td>
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<tr>
<td>USA</td>
<td>United States of America</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WIPO</td>
<td>World Intellectual Property Organization</td>
</tr>
<tr>
<td>WTO</td>
<td>World Trade Organization</td>
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</tbody>
</table>
EXECUTIVE SUMMARY

Background
Over the last decade, aggravated during the COVID-19 pandemic, medicine shortages have been increasing in Europe. Concerns have been raised that outsourcing of the production of active pharmaceutical ingredients (APIs) to Asia might have contributed to increased disruptions in the pharmaceutical supply chain. Among the policy measures to improve the reliance in the supply chain and thus to mitigate and prevent medicine shortages, reshoring of pharmaceutical production, in particular API manufacturing, to Europe, has been proposed.

Against this backdrop, the European Parliament requested a study to explore potential measures to facilitate the production of APIs in the EU Member States.

Aim
This study aims to map the current state-of-play

- with regard to national API production in Europe; including existing incentives and further measures put in place to encourage this production, and
- to identify challenges and areas of improvement to facilitate API production in Europe based on relevant documents, including studies, published at European and national levels.

Key Findings
Several policy documents (including some requested or produced by the European Parliament and the European Commission) and studies addressed the topic of production of APIs in Europe (frequently referred to as local production), as a potential solution to prevent or at least reduce medicine shortages. The documents tended to agree in considering reshoring of API production as a challenging endeavour, which would require high costs (in particular investment costs and workforce) and regulatory changes. Still, it was considered beneficial not only to strengthen the supply chain and reduce disruptions, but also to contribute to improved quality.

While the supply chains in the pharmaceutical sector are highly globalised, Europe still has some API production, mainly those of low production volumes, complex production processes. And the European API sector is considered highly competitive, given its technical know-how and strong workforce capacities.

This study presents three examples of local production in the European Union: The API production of penicillin in Kundl in Tyrol (Austria) has been in place for several decades. It was selected as an example for this report given the strategic decision to expand manufacturing. The Austrian government offered financial support to facilitate the expansion. The second example for local manufacturing of APIs concerns EuroAPI (a European API manufacturer originated from Sanofi), which is a public-private partnership through the involvement of the French government. Finally, Segens, another example from France, is financially supported by the French government, allowing it to expand its capacities and portfolio, to result in API production in the long run.

On behalf of the European pharmaceutical industry, there appears to be a willingness for considering reshoring of production of APIs to Europe if identified challenges were addressed.

While the study confirmed that for reshoring, financial support of governments to the pharmaceutical industry is a facilitating factor, it is not the only one. Further solutions proposed included: agreements
Potential measures to facilitate the productions of active pharmaceutical ingredients (APIs)

with local chemical suppliers (e.g. for key materials), the consideration of fee or tax benefits, the development of new production technologies (in order to accelerate automation and reduce labour costs), incentives to encourage the use of environmentally friendly technologies, the creation of training and programs to develop workforce needs and the alignment of existing policies.

However, also given some recent reshoring processes and the lack of the evidence on the impact as to what extent local API production can reduce the risk of shortages, policy-makers are cautioned against considering local production in every case as the sole solution. In particular, before taking any potential measures to facilitate reshoring of the production of APIs in Europe, some priority decisions should be taken to define the priority area of critical medicines and medical devices for which reshoring could be considered. Furthermore, investments to (financially) support local API production could be linked to conditions such as transparency in the supply chains, high social and environment standards and high quality of the APIs.
1. BACKGROUND

KEY INFORMATION

Medicine shortages pose an increasing challenge around the globe. Their causes are multi-fold given to the complexity of the globalised value chain. Key reasons for medicine shortages include:

- unexpected temporarily increased demands;
- disruptions in the supply chains;
- quality issues in production; and
- problems during transportation.

In the past, pharmaceutical production – including raw materials, active pharmaceutical ingredients (APIs) and final formulations (medicines) – has been increasingly moved towards Asia (mainly India and China), resulting in very few production sites in some cases.

In response, calls have been voiced to strengthen the resilience of health systems and to reduce the import dependency in Europe. One approach to reduce the dependency would be to reshore the production of pharmaceuticals – including APIs – to Europe.

This study explores potential measures that facilitate the production of APIs in Europe.

Access to medicines is a fundamental component of the right to health\(^1\). However, ensuring access to medicines remains a challenge globally\(^2\). One important access dimension is "availability"\(^3\). The availability of medicines may be impacted by several factors, including\(^4\):

- non-launch of medicines (markets are not considered attractive for suppliers);
- delayed launch (strategic behaviour of pharmaceutical companies in response of the external price referencing policy);
- withdrawal of medicines for safety reasons or business considerations; and
- shortages (i.e. disruptions in the supply chain).

Medicine shortages have increasingly become a concern all over the world, including Europe. The first reported medicine shortage affected insulin a century ago, and the extent of shortages intensified over the past 20 years. During the COVID-19 pandemic the issue became more visible and urgent, when


shortages for certain critical pharmaceuticals emerged\textsuperscript{5,6,7,8,9,10}.

The causes for shortages are complex, due to the intricately globalised pharmaceutical value chain\textsuperscript{11}. In general, reasons for shortages include\textsuperscript{12,13,14,15}.

- unexpected temporarily increased demands (e.g. during flu season);
- issues in the supply chain (e.g. limited number of suppliers due to high complexity of the production, making the supply chain less resilient);
- quality problems (e.g. contaminations during manufacturing); and
- disruptions during transportation (e.g. when it comes to freight issues, as happened in 2021 in the Suez Canal).

Until the 1950s, Europe was the global leader in medicines manufacturing. In the 1960s, the emerging economies of India and China started to set up pharmaceutical production capacities to cover their own needs and become independent from other countries, such as Europe and the USA. Over time, Indian and Chinese manufacturers became very competitive in the world market and exerted price pressure on manufacturers in the Western countries, resulting in a transfer of global production of pharmaceuticals (including APIs) towards Asia\textsuperscript{16,17,18}.

Thus, pharmaceutical production left Europe. This concerned medicines as finished products, raw materials and active pharmaceutical ingredients (APIs), which are the active ingredients in medicines. These changes have resulted in a globalisation of the pharmaceutical supply chain. An overview of the pharmaceutical supply chain is displayed in the figure below. As of 2021, China is the world's main supplier of raw materials, including key starting materials (KSMs), intermediates and APIs. While India is also a major producer of APIs, it is an even larger producer of finished products, particularly generics.

\textsuperscript{5} Heiskanen et al., 2017, The reasons behind medicine shortages from the perspective of pharmaceutical companies and pharmaceutical wholesalers in Finland, available at: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0179479.
\textsuperscript{6} Atif et al., 2019, Medicines shortages in Pakistan: a qualitative study to explore current situation, reasons and possible solutions to overcome the barriers, available at: https://bmjopen.bmj.com/content/bmjopen/9/9/e027028.full.pdf.
\textsuperscript{7} Anson and Taylor, 2020, Weak links: Instabilities and areas for improvement in the drug supply chain, available at: https://www.japha.org/article/S1544-3191(20)30120-5/fulltext.
\textsuperscript{12} Woo et al., 2008, The effect of globalization of drug manufacturing, production, and sourcing and challenges for American drug safety.
\textsuperscript{13} Charoo et al., 2019, Lesson Learnt from Recall of Valsartan and Other Angiotensin II Receptor Blocker Drugs Containing NDMA and NDEA Impurities, available at: https://link.springer.com/article/10.1208/s12249-019-1376-1.
\textsuperscript{14} Anson and Taylor, 2020, Weak links: Instabilities and areas for improvement in the drug supply chain, available at: https://www.japha.org/article/S1544-3191(20)30120-5/fulltext.
\textsuperscript{15} European Public Health Alliance, 2022, Why patients cannot access to medicines they need in Europe, available at: https://epha.org/why-patients-cannot-access-to-medicines-they-need-in-europe.
\textsuperscript{17} World Health Organization, 2017, China policies to promote local production of pharmaceutical products and protect public health, available at: https://apps.who.int/iris/rest/bitstream/1316049/1316049/retrieve.
\textsuperscript{18} World Health Organization, 2017, India policies to promote local production of pharmaceutical products and protect public health, available at: https://apps.who.int/iris/handle/10665/336750.
Therefore, India is dependent on imports for approximately 32% of its production needs, for which China is the major supplier\textsuperscript{19,20,21,22,23}.

Figure 1: Generic illustration of the pharmaceutical supply chain

Source: Authors’ own elaboration, based on Marrone (2023)\textsuperscript{24}.

Globally, one to five production sites with valid certificates of suitability of monographs of the European Pharmacopoeia (CEPs) are in place for more than half of all APIs (using CEPs, manufacturers can demonstrate that the quality of a substance is suitably controlled by the respective monograph of the European Pharmacopoeia). As a result, only a few manufacturers are responsible to ensure the production for Europe and worldwide\textsuperscript{25}.

As another challenge, when finished product manufacturers rely on subcontractors that in turn are dependent on a few raw material or API producers, the supply chain gets fragile\textsuperscript{26}.

Given these challenges, there have been discussions to reshore pharmaceutical production, including the production of APIs, to Europe\textsuperscript{27}.

Against this backdrop, the Committee on Environment, Public Health and Food Safety (ENVI) requested a study to explore potential measures that facilitate the production of active pharmaceutical ingredients (APIs) in the EU Member States.

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\textsuperscript{19} Bogaert et al., 2015, A Qualitative Approach to a Better Understanding of the Problems Underlying Drug Shortages, as Viewed from Belgian, French and the European Union’s Perspectives, available at: https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0125691&type=printable.


\textsuperscript{23} Hatton et al., 2022, Countries Manufacturing Pharmaceuticals for the US Market: A 10-Year Analysis of Public Data.


\textsuperscript{26} Heiskanen et al., 2017, The reasons behind medicine shortages from the perspective of pharmaceutical companies and pharmaceutical wholesalers in Finland, available at: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0179479.

2. METHODS

KEY INFORMATION

Aim: to map the state of affairs and to explore potential measures and initiatives to facilitate the production of active pharmaceutical ingredients (APIs) in the EU.

Approach: A literature search was conducted to identify relevant documents, with a focus on grey literature. A total of 83 documents were considered relevant for this in-depth analysis, of which 53 documents were considered for data extraction. The information gained by the literature was validated and supplemented by semi-structured interviews.

2.1. Aim and scope

The aim of this study is to map the current relevant literature on reshoring pharmaceutical production (e.g. requested and/or finalised by the Commission or other EU bodies) plus the production of active pharmaceutical ingredients (APIs) in Europe, and to explore potential measures and initiatives to facilitate the production of APIs in the EU Member States.

The various dimensions of the scope of the study and its investigated policies are described in Table 1.

Table 1: Dimensions of the scope of the in-depth analysis

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Products</td>
<td>Pharmaceutical active ingredients (APIs)</td>
</tr>
<tr>
<td>Settings</td>
<td>Different sectors in which policy measures may be taken (health, industrial policy, education, research, multi-sectorial policy)</td>
</tr>
<tr>
<td>Geography</td>
<td>EU and its Member States (but not exclusively limited to this region)</td>
</tr>
<tr>
<td>Timing</td>
<td>Any measures to facilitate the production of APIs and/or medicines (implemented ones, those in preparation and those under discussion)</td>
</tr>
</tbody>
</table>

Source: Authors' own elaboration.

2.2. Terminology

In the literature, various terms are used to describe bringing back the "pharmaceutical" production (to Europe). Information regarding this terminology can be found in the box below.
Box 1: Terminology regarding "reshoring"

Reshoring describes the act of bringing manufacturing back to a country. Possible synonyms that are used in the literature include backshoring or relocating. Terms like onshoring or nearshoring are also used as synonyms, but may be misleading, as nearshoring can also be interpreted as the outsourcing to a nearby country and onshoring can refer to the process of transferring different segments of a business to another company.

Hence, in this report the term "reshoring" is used to describe the process of bringing the production (of APIs) back (to Europe).

Source: Authors’ own elaboration.

Moreover, in this report, various terms are used to describe the type of production with regard to "locality". Information regarding this terminology can be found in the following box.

Box 2: Terminology regarding "locality"

When it comes to the "locality" of production, the following terms are used in this report:

- Local: used to describe a more close-by production. This can refer to a certain region (such as Europe, the EU or a country).
- National / domestic: used to describe the production in a (certain) country.

Source: Authors’ own elaboration.

2.3. Literature search

For identifying relevant literature, a systematic literature search for publications and a hand search for documents (such as grey literature) was conducted.

Relevant information from eligible documents was extracted and systematically included into tables. The single-data extraction method with verification was used, in which one researcher extracted the data and a second researcher checked the extracted data.

2.3.1. Search for scientific publications and studies (systematic search)

For the systematic literature review, a search in PubMed was conducted on 8th February 2023, which yielded a total number of 1,115 hits. The detailed search strategy is described in the ANNEX.

The titles and abstracts were screened by one researcher, and a total of 13 articles from this systematic search were selected for the in-depth analysis.
2.3.2. Search for documents and grey literature (hand search)

The systematic literature review was supplemented by a hand search, which was conducted from 3rd to 6th February 2023 on the following websites, using various search terms (search terms are listed in the ANNEX):

- European Parliament, the European Commission
- OECD
- WHO
- WTO, WIPO
- Google and Google Scholar
- Institutions in national EU Member States (partially done)
- Industry associations (pharmaceutical and wholesale):
  - At European level:
    - European Federation of Pharmaceutical Industries and Associations (EFPIA)
    - GIRP - European Healthcare Distribution Association
    - Medicines for Europe
  - At national level:
    - Bundesverband der pharmazeutischen Industrie e.V. (BIP; Germany)
    - Farma industria (Spain) and Farmindustria (Italy)
    - Interpharma (Switzerland)
    - Les Entreprises du Médicament (Leem; France)
    - Verband der pharmazeutischen Industrie Österreichs (PHARMIG; Austria)

Furthermore, the reference lists of four key documents were screened to identify potentially eligible literature.

From the hand search, a total of 70 documents were selected for the in-depth analysis.

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2.4. Interviews

To validate the information, to support the evidence base and to close any potential information gaps, two interviews with key informants were conducted (two independent researchers). The interviews were performed in parallel to the drafting of the report (but after the document analysis and literature review) to incorporate the additional information into the report.

The interviews were conducted as semi-structured interviews. Informed consent was taken, and the documentation of the interviews has been stored in line with data protection requirements.
3. RESULTS

KEY FINDINGS
A total of 43 relevant documents were identified for mapping, comprising:
- 10 key documents at EU level;
- 12 documents on supranational levels;
- 6 documents from industry; and
- 15 documents from other sources.

Key findings of these documents are:
- Medicine shortages are an increasing global concern.
- Since complex globalised pharmaceutical supply chains have been mentioned as one reason for shortages, reshoring of the pharmaceutical production to a more local level (in Europe) has been proposed as one measure to address shortages.
- Reshoring can be associated with some challenges, such as high costs (mainly labour and investments, e.g. to build production capacities).
- But reshoring was found to have some positive effects (e.g. decreasing import dependency from other countries and higher quality of production and products, such as APIs).

To describe the current situation of API production in Europe, 14 additional documents were considered relevant. To date, Europe is still strongly involved in API production (especially for complex APIs). Furthermore, efforts have been made to strengthen European API production. Three major initiatives to support API production in Europe were identified:
- Penicillin production by Novartis/Sandoz, supported by the Austrian government.
- EuroAPI: an initiative for European API production, with the involvement of the French investment bank.
- Seqens: extension of API production with financial support by the French investment bank.

3.1. Mapping of relevant documents
This section summarises relevant identified documents (including studies) that were requested and/or produced by EU bodies and institutions or published by other authors and organisations, including industry associations.

The issue of shortages has gained major public and political attention. It has been a priority in the EU and its Member States for many years and has been raised by various recent Presidencies of the Council. The European Parliament (EP) adopted several resolutions on access to medicines and on policy action to address shortages. The resolutions also considered the impact of the COVID-19 pandemic and proposed a reinforced role for the European Medicines Agency (EMA). Communications by the European Parliament and the European Commission also considered to improve the supply chain resilience in certain industries, including the bio/pharmaceutical industry, and specifically for the
supply of active pharmaceutical ingredients (APIs) in the EU\textsuperscript{32,33,34,35}. A key policy document in the field is the 2020 Pharmaceutical Strategy for Europe, which aims to balance ensuring access to affordable medicines for patients to address unmet medical needs and support competitiveness, innovation and sustainability of the EU’s pharmaceutical industry and the development of high quality, safe, effective and greener medicines. The Pharmaceutical Strategy for Europe is aligned with other core strategies, such as the Industry Strategy for Europe and the European Green Deal. To implement the Pharmaceutical Strategy for Europe, among others, a revision of the pharmaceutical legal framework (general pharmaceutical legislation, orphan and paediatric legislation legislation) is being prepared\textsuperscript{36,37,38,39}.

One aspect raised in the discussion of improving the supply chain resilience addresses reshoring the manufacturing of critical medicines and medical devices back to Europe, which was also put on the agenda by the German Presidency of the Council of the European Union in 2020\textsuperscript{40}.

The European Parliament outlined the need for more investments in the manufacture of APIs and pharmaceuticals (medicinal end products) in the EU, urging the European Commission and the Member States to introduce financial incentives - where appropriate - to preserve and expand the EU’s pharmaceutical industrial base, including for the production of APIs\textsuperscript{41,42}.

### 3.1.1. Key documents at EU level

A total of 10 key documents that were commissioned at EU level were identified. Most documents were published rather recently (in 2020 or later), however, two documents date back to 2009.

Table \ref{keydocuments} summarises the findings from the key documents at EU level. Detailed information extracted from these documents is provided in the ANNEX (Table \ref{annex_table}: Documents at EU level).

Several documents stressed the high import dependency regarding APIs from other countries, which is considered as a major cause for the supply chain disruptions. However, there is lack of empirical evidence to demonstrate that medicine shortages have solely been caused by the outsourcing of low-complex API production outside of Europe. Recommendations for strengthening the supply chains and

\begin{table}[h]
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\begin{tabular}{|c|c|}
\hline
Document & Reference \tabularnewline
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European Commission, 2019, Communication on The European Green Deal, available at: https://eur-lex.europa.eu/resource.html?uri=cellar:b828d165-1c22-11ea-8c1f-01aa75ed71a1.0002.02/DOC_1&format=PDF. \tabularnewline
\hline
\hline
\hline
\hline
\hline
\end{tabular}
\caption{Key documents at EU level}
\end{table}
Potential measures to facilitate the productions of active pharmaceutical ingredients (APIs) preventing medicine shortages include the diversification of production sites and regulatory modifications as well as changes in procurement procedures. It has been argued that local production in Europe can be facilitated through incentives (for industry) and workforce education.

Table 2: Overview of key documents at EU level

<table>
<thead>
<tr>
<th>Main topics</th>
<th>Documents</th>
<th>Challenges</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicine shortages</td>
<td>• De Jongh et al. (2021)43 • European Commission (2020)44 • European Parliament (2020)45</td>
<td>• Increase in reported shortages, but inconsistencies and limitations in reporting of shortages</td>
<td>• Diversification of tenderers and public procurement processes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lack of data to conclude whether or not outsourcing of API production is a risk factor for shortages</td>
<td>• Strengthening the production of medicines through financial incentives (e.g. subventions or grants)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• De Jongh et al. (2021)43</td>
<td>• Cooperation between countries</td>
</tr>
<tr>
<td>(Local) production</td>
<td>• European Commission, Directorate-General for Communication (2021)46</td>
<td>• Most medicines in Africa are imported</td>
<td>• Strengthening training of workforce</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Transfer of technologies</td>
</tr>
<tr>
<td>Other (supply chain, etc.)</td>
<td>• Szczepański, M. (2020)47 • ECORYS, Cambridge Econometrics et al. (2014)48, 49 • European Commission and Directorate-General for Health and Food Safety (2020)50 • EU Parliament (2021)51 • EPHA (2022)52</td>
<td>• High dependency on imports from China • High production and registration costs in Europe • European manufacturers mainly produce highly complex, specialised medicines</td>
<td>• Incentivising reshoring (e.g. financial incentives) • Diversification of production sources • Expanding domestic production and the use of innovative production techniques • Risk management strategies and guidelines • Optimising public procurement practices • Strengthening the cooperation of the public sector with the private sector in EU Member States • Smarter and more efficient regulatory processes • Increasing transparency (e.g. supply chain and prices)</td>
</tr>
</tbody>
</table>

Source: Authors’ own elaboration.

3.1.2. Other relevant documents

This section summarises other relevant documents (including studies) that were identified. These are.

- Documents prepared by supranational organisations (e.g. WHO, OECD, WTO) or at national level
  ⇒ Table 3
- Documents prepared or commissioned by industry and their associations (e.g. Medicines for Europe)
  ⇒ Table 4
- Documents by other authors (e.g. independent studies published in peer-reviewed journals)
  ⇒ Table 5

More detailed information of these documents can be found in the ANNEX (Table 11 to Table 13).

Documents are not limited to Europe, since challenges and potential solutions concerning domestic production in non-European countries were considered of interest for this report. This allows for learning from their lessons.

Supranational and national level

A total of 12 documents have been identified that were prepared by supranational organisations or at national level. Five of these documents were published by the WHO and two by the US government.

Results show that local production is associated with higher costs and increased efforts due to higher regulatory standards. Thus, local production might not be feasible for single countries, and so this requires cooperation to develop joint solutions at EU level to achieve sustainable supply chains.

At the time of this in-depth analysis, a Technical Support Implementation (TSI), requested by the Austrian government, is ongoing. It is entitled "Ensuring Patient Access to Medicines in Austria and the EU by Improving the Pharmaceutical Value Chain" and aims to identify and implemented policy solutions, which may also address pharmaceutical production (results are expected to be disseminated in autumn 2023)53.

The White House, 2021,
Strengthening local production of medicines and other health technologies to improve access
available at: https://apps.who.int/iris/bitstream/handle/10665/44713/9789241502351_eng.pdf?sequence=1&isAllowed=y.

Bumpas and Betsch, 2009,

The White House, 2021,
FACT SHEET: Biden-Harris Administration Announces Supply Chain Disruptions Task Force to Address Short-Term Supply Chain Discontinuities, available at: https://apps.who.int/iris/rest/bitstreams/1316049/retrieve.

The White House, 2021,

World Health Organization, 2021,
China policies to promote local production of pharmaceuticals and protect public health, available at: https://apps.who.int/iris/handle/10665/36750.

World Health Organization, 2021,

OECD, 2020,

### Industry and their associations

Six documents were included that were prepared or commissioned by the industry and its respective associations.
The documents highlighted that the fragmented supply chains and the low number of API manufacturers constitute a major challenge for Europe. Even though local production might contribute to a reduction in medicine shortages, the production of APIs in Europe is associated with high costs and strict regulations. Therefore, fostering partnerships with other countries to facilitate production and benefit from shared infrastructure was discussed as a solution in the long term. Technology transfer was suggested as another approach that may contribute to more robust supply chains.

Table 4: Overview of documents from industry and their associations

<table>
<thead>
<tr>
<th>Main topics</th>
<th>Documents</th>
<th>Challenges</th>
<th>Solutions and conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicine shortages</td>
<td>Cogan et al. (2018)67</td>
<td>Fragmented and complex supply chains</td>
<td>Strengthening local production and transfer of technologies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Improvement of flexibility and communication</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>regarding stock management of pharmaceutical companies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increased collaboration between suppliers, governments and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>all stakeholders</td>
</tr>
<tr>
<td>(Local) production</td>
<td>CII (2021)68</td>
<td>High production costs (e.g. electricity, logistics, set-up costs)</td>
<td>Creating production clusters with shared infrastructure</td>
</tr>
<tr>
<td></td>
<td>Medicines for Europe (2021)69</td>
<td>Limited availability of raw materials</td>
<td>Improved collaboration between academia and industry</td>
</tr>
<tr>
<td></td>
<td>MundiCare (2020)70</td>
<td>Scarcity of API manufacturers</td>
<td>Reforms in pricing and reimbursement (e.g. consider local</td>
</tr>
<tr>
<td>Other (supply chain, etc.)</td>
<td>EFPIA (2022)71</td>
<td>European supply chains mostly concern</td>
<td>Foster partnerships (e.g. with the US)</td>
</tr>
<tr>
<td></td>
<td>Medicines for Europe (2020)72</td>
<td>complex medicines</td>
<td>Use of digitalization for technology transfers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>European cooperation</td>
</tr>
</tbody>
</table>

Source: Authors’ own elaboration.

A survey conducted with companies from different industry sectors (including the pharmaceutical industry) highlighted that from their perspective, the operating costs in Europe due to higher personnel costs and the lack of supplier bases that are not far away (such as for key material) are considered as major hurdles to reshoring production in Europe (see figure below)73.

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68 Confederation of Indian Industry and KPMG, 2020, Indian API Industry – Reaching the Full Potential, available at: https://www.cii.in/PublicationDetail.aspx?enc=swL3yNiPL0AFvxDG0sBN7Hj1d8H2kOpT1dExgTCl6fm91IMdHujZqC-cWq7n+yLBxJOVxwNnAulfsbScIRhV15jUCL0V+HLt0qsgmVBBV4KtedM9nQAKULAC1cy+79C1KSokxzaEM7barF+txNBGMUuZq+tTzaU6KEk=.
Potential measures to facilitate the productions of active pharmaceutical ingredients (APIs)

Figure 3: Barriers to reshoring – results from a survey with companies

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low capacities of supplier bases</td>
<td>15%</td>
</tr>
<tr>
<td>Required investments</td>
<td>20%</td>
</tr>
<tr>
<td>Uncertain supply chain dynamics</td>
<td>15%</td>
</tr>
<tr>
<td>Lack of supplier base</td>
<td>35%</td>
</tr>
<tr>
<td>Operating costs</td>
<td>35%</td>
</tr>
</tbody>
</table>

Source: BCI Global (2022)**, survey was conducted with companies across sectors.

Other documents

The analysis of 15 documents from other authors similarly revealed that the high import dependency from other countries remains a major challenge in Europe, in particular for high volume, low complexity APIs. The concentrated production of APIs in non-European countries was found to be associated with a number of risks, including long delivery times, lower quality of products or geopolitical disruptions. Therefore, reshoring the production of critical APIs back to Europe might be a solution to prevent shortages and strengthen the supply chain. Changes in the regulatory frameworks, use of innovative production techniques and joint initiatives might be necessary to facilitate the process of reshoring API production.
Table 5: Overview of other documents (mainly studies)

<table>
<thead>
<tr>
<th>Main topics</th>
<th>Documents</th>
<th>Challenges</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicine shortages</td>
<td>Beck et al. (2019)\textsuperscript{74}, Bogaert et al. (2015)\textsuperscript{75}, Heiskanen et al. (2017)\textsuperscript{76}</td>
<td>Limited number of suppliers, Dependency on foreign manufacturers, Long delivery times due to import, High fluctuations in demand as a cause for shortage</td>
<td>Better coordination and cooperation at the EU level</td>
</tr>
<tr>
<td>(Local) production</td>
<td>Barbieri et al. (2022)\textsuperscript{77}, Cherian et al. (2021)\textsuperscript{78}, Marrone et al. (2023)\textsuperscript{79}, Raza et al. (2021)\textsuperscript{80}, Roehr, B. (2022)\textsuperscript{81}, Sanchez et al. (2021)\textsuperscript{82}</td>
<td>Market unattractiveness in Europe for local production, Conflict between the aim to secure supply and cost-efficient production of medicines, Increased quality risks for offshored pharmaceuticals, Complexity of manufacturing, High risks for offshoring (e.g. geopolitical disruptions)</td>
<td>Diversification of suppliers, Multicriteria decision-making strategy for local production, Develop minimum local production capacities (for critical medicines), Technological innovation (e.g. continuous flow production technique), Joint initiatives (industry and non-industry) for reshoring production to Europe, Risk management and assessment strategies for local production, Enhancement of regulatory and pricing for production (e.g. tax incentives)</td>
</tr>
<tr>
<td>Other (supply chain, etc.)</td>
<td>Berrer et al. (2020)\textsuperscript{83}, Franca et al. (2021)\textsuperscript{84}, Goerg et al. (2020)\textsuperscript{85}</td>
<td>High costs for reshoring, Import dependency, Most low-complexity, high volume APIs have been outsourced</td>
<td>Higher efforts in research and development, Strengthen regulatory framework (e.g. subventions, tendering, trade</td>
</tr>
</tbody>
</table>


\textsuperscript{75} Bogaert et al., 2015, A Qualitative Approach to a Better Understanding of the Problems Underlying Drug Shortages, as Viewed from Belgian, French and the European Union’s Perspectives, available at: https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0125691&type=printable.

\textsuperscript{76} Heiskanen et al., 2017, The reasons behind medicine shortages from the perspective of pharmaceutical companies and pharmaceutical wholesalers in Finland, available at: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0179479.


\textsuperscript{80} Raza et al., 2021, Wirtschaftspolitische Maßnahmen zur Erhöhung der Versorgungssicherheit bei kritischen Gütern, available at: https://emedien.arbeiterkammer.at/viewer/ppnresolver?id=AC16386230.

\textsuperscript{81} Roehr, 2020, Bringing drug production home: how the US is rebuilding the drug supply chain after covid-19, available at: https://www.bmj.com/content/bmj/370/bmj.m3393.full.pdf.

\textsuperscript{82} Sanchez and Muzzio, 2021, Reshoring Pharmaceutical Manufacturing to the US: Can We Do It?, available at: https://www.pharmtech.com/view/reshoring-pharmaceutical-manufacturing-to-the-us-can-we-do-it.


### 3.2. Current situation of active pharmaceutical ingredient (API) production

#### 3.2.1. Overview of API production in Europe

In 2019, nearly 36% of API manufacturing sites were located in Europe, whereas 55% of manufacturing sites were in Asia (see figure below). In value terms, the EU’s share of global generic API production was 24%, compared to 66% in Asia Pacific (India and China). In 2021, China brought 18 new active substances for the first time onto the market (worldwide) and nearly equalled Europe (19 new active substances).

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Nonetheless, Europe and the EU are still a strong competitor, especially when it comes to global pharmaceutical manufacturing leadership. Today, European manufacturers are specialised in APIs with low production volumes, technologically complex production processes and products with high quality requirements.\textsuperscript{89,90}

In contrast, many manufacturers in India and China have a relatively small API portfolio. Indian manufacturers tend to be larger and more focused on high-volume APIs. The production of older APIs tends to be strong in Europe and the migration to Asia is still low for these APIs. Newer APIs have a high proportion of Asian manufacturers and/or migration to Asia is faster. Moreover, most APIs are either produced mainly in Europe or Asia, only for a few APIs is the production balanced between Europe and Asia. For more than half of the APIs that are placed in the EU market, there are only one to five manufacturers with a valid CEP globally.\textsuperscript{91}

Furthermore, for certain indications, the share of APIs (when it comes to APIs with valid Certificates of Suitability of Monographs of the European Pharmacopoeia) production in Europe is higher (see figure 5 below).\textsuperscript{91}

For some APIs (e.g. Benserazide and Propofol) the demand is fully covered by European production. In contrast, there are other APIs that are exclusively produced in Asia (e.g. Simvastatin).\textsuperscript{91}

Figure 5: Certificates of Suitability of Monographs of the European Pharmacopoeia for APIs

Source: MundiCare (2020)\(^9\).

Abbreviations: ROA – rest of Asia; ROW – rest of world.

ATC classifications: A – Alimentary tract and metabolism; B – Blood and blood forming organs; C – Cardiovascular system; D – Dermatologicals; G – Genito urinary system and sex hormones; H - Systemical hormonal preparations, excl. sex hormones and insulins; J – Antiinfectives for systemic use; L – Antineoplastic and immunomodulating agents; M – Musculoskeletal system; N – Nervous system; P – Antiparasitic products, insecticides and repellents; R – Respiratory system; S – Sensory organs.

There is at least one API production site in nearly every European country (see figure below). The majority of production sites are in:

- Italy (63 sites)
- Germany (54 sites)
- Spain (44 sites)
- France (43 sites)

Moreover, in the UK, in Ireland and Switzerland, there are also a high number of production sites (35, 28, 24, respectively). Overall, there are around 440 API production sites in Europe, producing 554 APIs\(^9\),\(^9\).

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3.2.2. Existing incentives and measures to promote API production in Europe

Relocating manufacturing operations back to Europe is a growing trend in nearly every industry sector, including the pharmaceutical sector. Several pharmaceutical manufacturers in Europe have announced plans for new in-country API development and manufacturing capabilities.34

Three government initiatives to support API production in an EU Member State were identified:

- The expansion of the local API production at the manufacturing site for penicillin in Kundl in Tyrol (Austria) is partly funded by the Austrian government (50 million Euro from government, 100 million Euro from industry).35

- EuroAPI (a European manufacturer of APIs, originated from Sanofi), where the French government holds a share of 12% through the French public investment bank "EPIC Bpifrance". The bank committed to a lock-up of 24 months on EuroAPI shares, starting as from 17th June 2022.36

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Potential measures to facilitate the productions of active pharmaceutical ingredients (APIs)

- Seqens, with the financial support of the French government (94 million Euro in 2021) through the investment bank "EPIC Bpifrance", continuously extending its capacities and portfolio. The multi-purpose units will produce non-good manufacturing practice (GMP) intermediates in the short term, and APIs in the long term\(^9\).

Detailed information is summarised in Table 6.

There are also other current initiatives to incentivise the pharmaceutical value chain (at least in parts), which are not mentioned in this report, as these are neither involving public authorities (e.g. exclusively industry driven) nor related to API production. One such initiative is the "Lighthouse Project –Industry 5.0" in Ireland - funded in part by the Irish government – and doing research in innovating manufacturing processes\(^9\).

\(^9\) Seqens, 2021, SK Capital becomes the new majority shareholder of Seqens – Q&A, available at:  

\(^9\) The European Chemical Industry Council, 2022, Landscape of the European Chemical Industry: Ireland, available at:  
https://cefic.org/a-pillar-of-the-european-economy/landscape-of-the-european-chemical-industry/ireland/
Table 6: Overview of government initiatives to promote API production in Europe

<table>
<thead>
<tr>
<th>Initiative</th>
<th>Overview</th>
<th>Country</th>
<th>Year</th>
<th>API / medicines affected</th>
<th>Stakeholders involved</th>
<th>Core nature of incentive / measure</th>
<th>Public resources spent</th>
<th>Impact / success</th>
<th>Challenges and issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kundl99,100,101 (Novartis/Sandoz)</td>
<td>Plant in Kundl (Tyrol)</td>
<td>Austria</td>
<td>2021 (announced)</td>
<td>Penicillin</td>
<td>Novartis/Sandoz Austrian government</td>
<td>Subventions by state</td>
<td>50€ million (100€ million from industry) (announced)</td>
<td>• Increase in production • Potential to produce penicillin for the entire demand in Europe</td>
<td>Unclear (long-term data missing)</td>
</tr>
<tr>
<td>EuroAPI102,103,104 (Sanofi)</td>
<td>Founding initiative for an European API production company</td>
<td>France</td>
<td>2021</td>
<td>Steroids, Alkaloids, Sarans, Antihistamines, Antipyretics, Vitamin B12, Anti-infectives, Prostaglandins</td>
<td>Shareholders: Sanofi (30,1%), EPIC Bpifrance (12%), L’Oréal (5,5%), Free float (52,4%)</td>
<td>Share (12%) by state investment bank Bpifrance (through “French Tech Souveraineté”)</td>
<td>unclear</td>
<td>• $770 million sales for APIs in 2021 • Specialised production • Capable of producing &gt;80% of new drugs • Building additional capacity for vitamin B12, prostaglandins &amp; hormones • Multiple growth avenues including cross-selling, pricing enhancements, new clients, broader repatriation trends</td>
<td>Agility and responsiveness to demand</td>
</tr>
</tbody>
</table>

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103 Scott, 2022, EuroAPI is ready to emerge from Sanofi’s shadow, available at: https://cen.acs.org/articles/100/13/EuroAPI-ready-emerge-Sanoﬁs-shadow.html.
### Potential measures to facilitate the productions of active pharmaceutical ingredients (APIs)

<table>
<thead>
<tr>
<th>Initiative</th>
<th>Overview</th>
<th>Country</th>
<th>Year</th>
<th>API / medicines affected</th>
<th>Stakeholders involved</th>
<th>Core nature of incentive / measure</th>
<th>Public resources spent</th>
<th>Impact / success</th>
<th>Challenges and issues</th>
</tr>
</thead>
</table>
| Seqens105, 106, 107, 108, 109 | Continuously extending its capacities and portfolio with co-funding by French government | France | 2022 | • Paracetamol  
• Others | Shareholders:  
• SK Capita  
• Bpifrance,  
• Nov' Santé Actions Non Cotées  
• Mérieux Equity Partners  
• Ardian  
• Eximium | Subvention by state investment bank Bpifrance | 94€ million in 2021 | • Capacity to produce 10,000 tonnes of paracetamol per year  
• High-performance, innovative and competitive installation  
• €1 billion in sales, 24 industrial sites, 7 R&D centers and more than 3,000 employees | unclear (long-term data missing), in 2020 still depending on Asian intermediates |

Source: Authors’ own elaboration.

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4. CONCLUSIONS AND RECOMMENDATIONS

KEY INFORMATION
At the time of this analysis, the European API production appears to be competitive, meaning that technical know-how and production and workforce capacities are (still) available. However, there is the ambition to strengthen the local pharmaceutical production base in Europe.

Before implementing any measures to facilitate the production of active pharmaceutical ingredients (APIs), some arguments have to be taken into account for the decision making, such as prioritising (critical APIs first) and considering the whole pharmaceutical value chain and not exclusively focusing on the production of APIs.

The EU has undertaken first steps in order to increase local API production in Europe. However, targeted incentives still have to be implemented and various challenges and obstacles have to be addressed by suitable measures.

4.1. Summary of findings and conclusions
The analysis confirmed that reshoring of production is highly topical. While the discussions on reshoring are not limited to the pharmaceutical sector, it has a particular relevance in this field, since supply chains in the pharmaceutical industry are more global than in other sectors, and a concentration in one region (Asia) to source materials has developed. The vulnerability of the supply chains over the past years has become particularly evident during the Covid-19 pandemic, when shortages of some critical medicines and medical devices were experienced.

This has motivated policy makers and stakeholders to consider a diversification of the production sites to strengthen the supply chain resilience and efficiency in this complex and globalised setting. In addition, considerations have been made to move away from the lowest cost paradigm in production and supply in favour of security of supply, higher quality, improved flexibility to react to short-term changes in demand, and the opportunity for governments to steer production to most critically needed pharmaceuticals and devices. Furthermore, local production is considered beneficial for reducing transportation costs and time, which ensures faster and more reliable deliveries.

With regard to the challenges associated with reshoring, higher operating costs in Europe (e.g., due to higher personnel costs) and lack of suppliers based in Europe to source key material for API production are among the most commonly mentioned barriers. In addition, pharmaceutical companies reported to not have considered reshoring because it would be time-intensive and would imply significant financial investments to identify and set up new sites. Furthermore, planning and establishing (new) production facilities requires taking key management decisions and coping with national regulations.

With regard to the cost factor, Central and Eastern European countries (e.g., Czech Republic, Poland, Hungary) may likely be potential candidates for new production locations in Europe given their lower personnel costs. In practice, however, higher-income countries, such as Germany, the Netherlands and Belgium have also been mentioned as attractive production locations. It has been argued that new technologies will lead to an increase in automation and robotisation, and as a result personnel costs
may play a lower role\textsuperscript{110}.

From statements made and documents published by industry, it can be concluded that the \textbf{pharmaceutical industry} would be in favour of more local production of APIs and medicines in Europe, under the condition that governments are committed to facilitate the production in Europe. This would include, in particular, financial support by governments (e.g., pre-financing investments) to reduce the financial risk for pharmaceutical companies. However, non-financial support is also considered relevant, such as speeding up administrative and regulatory procedures.

Table 7 summarises challenges associated with reshoring, as well as potential solutions as identified in the literature.

Table 7: Challenges of reshoring and their potential solutions

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Description</th>
<th>Potential solution</th>
</tr>
</thead>
</table>
| Sourcing of intermediate or key materials | (Key) materials needed for API synthesis should come from reliable (and regional) sources | • Supply agreements with local chemical suppliers  
• Development of synthesis design for materials availability |
| Fiscal | Impact of local fees and taxes | • Federal or local governments need to consider fee or tax benefits for regionally sourced and produced products |
| Technology | Implementation of alternative manufacturing procedures and use of advanced technologies to reduce personnel costs | • Acceleration of automation and robotisation  
• Development of technologies, such as continuous manufacturing (CM) and process analytical technology (PAT) adapted to pharmaceutical manufacturing requirements  
• Use of strategies for hybrid CM and batch operations |
| Environment | API manufacturing use of solvents and their waste generation and handling | • Operations that are designed to minimise the use of solvents and waste generation  
• Provide local and federal economic incentives to encourage the use of environmentally friendly technologies |
| Workforce | There is limited (skilled) workforce availability for API manufacturing | • Academia can contribute to the creation of training and academic programs to address workforce needs |

### 4.2. Recommendations

Governments that aim to facilitate the productions of APIs are encouraged to first consider the following points before implementing any measures:

- It should be specified which APIs of which medicines are relevant or critical for patients in Europe. These APIs need prioritisation in the facilitation of local production.

- After prioritisation, it is recommended that an evaluation should be carried out to determine for which APIs the production can be reshored to Europe. This evaluation would need to consider several perspectives, such as economic parameters (to define the return on investment) and feasibility of reshoring.

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• The focus of reshoring should not exclusively lie on APIs to prevent medicine shortages:
  o The **supply of key materials to produce these APIs** needs to be ensured (e.g. through local and/or diversified suppliers)
  o The **production of the medicines** (finished products / formulations) should also be ensured (e.g. through local and/or diversified production)

• Initiatives to support or boost local production should not exclusively focus on financial incentives, but should also **consider further dimensions**, such as administrative and regulatory processes, to **ease and shorten the reshoring process** (e.g. authorities could assist manufacturers in regulatory processes).

• Incentives to support local production (especially financial incentives) could be linked to conditions, such as full transparency in the supply chains, fostering high social and environment standards and high quality of the production of APIs.

• It should be considered that further countries (mainly China, India and the USA) are also undertaking efforts to strengthen or intensify local production. These efforts might result in increased competition between countries.

In addition, **automatisation and technology** of the production process could be supported, as it would allow reducing operating costs (given higher personnel costs in Europe compared to Asian countries). To date, the pharmaceutical supply chain relies partly on outdated technology and methods that are incompatible with current global standards. Moreover, it creates an unpredictable environment. To make the pharmaceutical supply chain more competitive, companies should be encouraged to adopt new manufacturing techniques, such as continuous manufacturing (CM). Continuous manufacturing, along with process analytical technologies (PAT) are expected to expand manufacturing capacity and lower operating costs, with real-time quality control capabilities.

Furthermore, when it comes to pricing and reimbursement (and tendering) of medicines, not only the **price** but also the manufacturing location of key materials, APIs and the medicines themselves, could be a decision criterion (e.g. higher prices could be accepted when a medicine and its components are locally produced).

To create and foster a better pharmaceutical supply chain, transparency is crucial. One solution to **improve transparency** is a supply chain with local suppliers in order to verify the quality and availability of products. Transparency is also important to better grasp any issues or interruptions of the supply chain and to adequately and timely respond.

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117 Stauffer et al., 2018, Raw material variability of an active pharmaceutical ingredient and its relevance for processability in secondary continuous pharmaceutical manufacturing.
118 Markarian, 2021, Advanced Manufacturing Technologies Shift Outside the Box, available at: https://cdn.sanity.io/files/0vv8moc6/pharmtech/54b38663b93f237189318ae9114feb099e678ec0.pdf/PharmTech_NA_April2021_wm.pdf.
As the global economy relies on a global supply chain, it is not reasonable to expect that the whole production will be or should be localised in Europe. However, it appears feasible to build on the European manufacturing footprint, to invest in technological leadership and diversify the supply chain.

Europe and the European Union appear to be committed to achieving multiple policy objectives for medicines: to increase sustainability for patients, healthcare systems and the environment, and to strengthen supply chain resilience and therefore EU manufacturing competitiveness.

These commitments are reflected in several resolutions or strategy papers (e.g. Pharmaceutical Strategy for Europe, European Green Deal, EU4health), alignment of authorities (e.g. implementation of European Health Emergency Response Authority / HERA\textsuperscript{122} or the reinforced role of the EMA) and updated state-aid criteria (e.g. to enable national tax deductions, API and medicines development incentives or other facilities).


REFERENCES


• Confederation of Indian Industry and KPMG, 2020, *Indian API Industry – Reaching the Full Potential*. New Delhi: Confederation of Indian Industry. Available at: https://www.cii.in/PublicationDetail.aspx?enc=swL3yNIPL0AFuvDG0sBN7Hxj1dBiH2kOp4TdEXgdTCIl6fm91IMdHjrZ9Cw+z+Wq7n+yLBxJ0VxpwNnAutfbs9cIRXh1SUCL0Vi+HLfoogSmgVBBDVKtedM9nOAKULAc1cy+79C1K5oksxZA7M7baxF+txNBGmUuZ9q+fTzaU6Ke+k=.


Potential measures to facilitate the productions of active pharmaceutical ingredients (APIs)


• European Public Health Alliance (2022) Why patients cannot access to medicines they need in Europe. Available at: https://epha.org/why-patients-cannot-access-to-medicines-they-need-in-europe/


Potential measures to facilitate the productions of active pharmaceutical ingredients (APIs)


• Roehr B, 2020, Bringing drug production home: how the US is rebuilding the drug supply chain after covid-19. BMJ 370. Available at: https://www.bmj.com/content/bmj/370/bmj.m3393.full.pdf.


• Sanofi and EuroAPI, 2022, EuroAPI Capital Markets Day. Available at: https://www.euroapi.com/sites/default/files/2022-06/EUROAPI-CMD-Presentation_April%202022.pdf.


• Scott A (2022) EuroAPI is ready to emerge from Sanofi’s shadow. (accessed 22nd February 2023). Available at: https://cen.acs.org/business/outsourcing/EuroAPI-ready-emerge-Sanofis-shadow/100/i13


Potential measures to facilitate the productions of active pharmaceutical ingredients (APIs)


ANNEX

Search strategies

Systematic literature search

Table 8: Search strategy for systematic literature search

<table>
<thead>
<tr>
<th>Search</th>
<th>Query</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>#5</td>
<td>Search: #3 AND #4</td>
<td>1,115</td>
</tr>
<tr>
<td>#4</td>
<td>Search: &quot;active pharmaceutical ingredient**&quot; OR pharmacon OR pharmakon</td>
<td>5,421</td>
</tr>
<tr>
<td>#3</td>
<td>Search: #1 AND #2</td>
<td>1,295,432</td>
</tr>
<tr>
<td>#2</td>
<td>Search: production OR manufactur* OR &quot;supply chain**&quot; OR &quot;value chain**&quot;</td>
<td>3,674,458</td>
</tr>
<tr>
<td>#1</td>
<td>Search: <em>shor</em> OR relocat* OR local OR domestic OR national OR europe* OR france OR germany OR italy OR switzerland OR spain</td>
<td>9,635,423</td>
</tr>
</tbody>
</table>

Source: Authors' own elaboration.
Hand search

Table 9: Search terms and strings for hand search

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search terms</td>
<td>reshor*, &quot;active pharmaceutical ingredient*&quot; OR &quot;API*&quot;, &quot;industry&quot;, &quot;production&quot; (in combination with &quot;local&quot;, &quot;domestic&quot; and &quot;European&quot;), &quot;Europe&quot;; a more detailed search strategy will be developed. - Further: medicine*, manufactur*, pharmaceutical*, drug*</td>
</tr>
<tr>
<td>Search strings</td>
<td>• API AND production AND Europe</td>
</tr>
<tr>
<td></td>
<td>• Active pharmaceutical ingredient AND production</td>
</tr>
<tr>
<td></td>
<td>• Active pharmaceutical ingredient AND production AND Europe</td>
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<tr>
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<td>• Active pharmaceutical ingredient AND European production</td>
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<tr>
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<td>• Active pharmaceutical ingredient AND local production</td>
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<tr>
<td></td>
<td>• Active pharmaceutical ingredient AND domestic production</td>
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<tr>
<td></td>
<td>• Active pharmaceutical ingredient OR medicine* AND industry</td>
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<td></td>
<td>• Active pharmaceutical ingredient OR medicine* AND industry AND Europe</td>
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<tr>
<td></td>
<td>• Reshor* AND medicine* OR Active pharmaceutical ingredient AND production</td>
</tr>
<tr>
<td></td>
<td>• Reshor* AND medicine* OR Active pharmaceutical ingredient AND industry</td>
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<tr>
<td></td>
<td>• Medicine* AND production AND Europe</td>
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<tr>
<td></td>
<td>• Medicine* AND European production</td>
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<tr>
<td></td>
<td>• Medicine* AND local production</td>
</tr>
<tr>
<td></td>
<td>• Medicine* AND manufactur* AND/OR Europe</td>
</tr>
<tr>
<td></td>
<td>• Active pharmaceutical ingredient and manufactur* AND/OR Europe</td>
</tr>
<tr>
<td></td>
<td>• Medicine shortage* AND Europe</td>
</tr>
<tr>
<td></td>
<td>• Medicine shortage* AND production AND Europe</td>
</tr>
<tr>
<td>German search terms</td>
<td>Wirkstoffproduktion AND Europa</td>
</tr>
<tr>
<td>and strings</td>
<td>Versorgungsengpass* AND Europa</td>
</tr>
<tr>
<td></td>
<td>Versorgungsengpass* AND Europa AND Produktion</td>
</tr>
<tr>
<td></td>
<td>Arzneimittelproduktion AND Europa</td>
</tr>
</tbody>
</table>

Source: Authors’ own elaboration.
**Detailed information from relevant documents**

Table 10: Documents at EU level

<table>
<thead>
<tr>
<th>Date</th>
<th>Commissioner</th>
<th>Author(s)</th>
<th>Main theme</th>
<th>Content</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| November, 2021     | European Parliamentary Research Service           | Szczepański, M.¹²³                       | Resilience of global supply chains              | • Generally, Europe is highly involved in global production chains.  
  • During Covid-19, goods exported from Asia were most affected from shortages. These shortages caused limitations in productions in two in five manufacturers in Europe.  
  • Potential policy actions to strengthen supply chains include:  
    o Incentivizing reshoring and nearshoring  
    o Diversification of import  
    o Expanding domestic production (industrial alliances at EU level)  
    o Public funding or financial incentives (e.g. corporate tax exemption for manufacturers who relocate for a certain time span)  
    o Risk management strategies and guidelines, especially in highly effected sectors (e.g. pharmaceutical industry)  
    o Public procurement to establish stable demand  
    o Cooperation with the private sector and like-minded countries (e.g. through the European Cluster Collaboration Platform or the Enterprise Europe Network)  
  • Currently, the EU is implementing a policy mix which targets the increase of domestic capacity, support trade environments and diversify suppliers. | Implementing a variety of policy actions at different levels may increase the resilience of global supply chains. |
| 2021               | European Parliament’s Directorate-General for External Policies of the Union | Raza et al.¹²⁴                           | Reshoring production to Europe                  | • The discussion on reshoring production has emphasized the importance of diverse production sites and suppliers as well as high-quality monitoring systems.  
  • Literature shows that reshoring happens more often, mostly by larger companies in high- und medium-tech industries. Impacts, however, are limited on the EU economy thus far.  
  • Drivers for reshoring include flexibility, proximity and quality.  
  • Literature suggests that high-tech industries are most likely to reshore to Europe.  
  • The reshoring of previously offshored products (including API) are not likely. Reasons include higher wages, supplier networks, high standards for sustainability in Europe and economies of scale.  
  • Recommendations include establishing minimum production capacities in the EU for certain products where bottlenecks are likely to occur. The manufacturing of new products on the EU market should be promoted. | Reshoring production to Europe may be relevant for specific critical sectors and products where bottlenecks occur. |
| December, 2021     | European Commission Directorate-General for Health and Food Safety Technopolis Group, Ecorys B.V., Milieu Law & Policy Consulting | De Jongh et al.¹²⁵                         | Medicine shortages                              | • Member States lack standardization in information sharing of shortages. Nevertheless, reported shortages have increased since approximately ten years.  
  • Due to inconsistencies and limitations in reporting of shortages, detecting the causes remains a major challenge. With the reported data, around 50% of shortages in Member States can be traced back to problems in manufacturing and quality.  
  • There is not enough available data to sufficiently address the outsourcing of pharmaceutical production (including API production) and its distribution as possible risk factors for shortages in the EU. | Medicine shortages will remain an essential topic in Europe. Systemic changes are required to solve root causes of the shortages and improve the situation in the long term. There is not enough data to determine whether outsourcing is a necessary strategy. |

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### Table: Medicines Shortages and Policy Recommendations

<table>
<thead>
<tr>
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<th>Commissioner</th>
<th>Author(s)</th>
<th>Main theme</th>
<th>Content</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>December, 2009</td>
<td>ECORYS Research and Consulting</td>
<td>Cambridge Econometrics, CES IPO, ECORYS IDEA Consult, Teknologisk Institut</td>
<td>Competitiveness of the EU Market and Industry for Pharmaceuticals – Vol. I and Vol II</td>
<td>• Diversification of tenderers and public procurement processes are included as recommendations to decrease shortages of medicines.</td>
<td>Efficiency of the European pharmaceutical market can still be substantially improved by designing smarter and efficient regulatory processes.</td>
</tr>
<tr>
<td>2020</td>
<td>European Parliament</td>
<td>Press Release</td>
<td>Strengthening the EU pharmaceutical policy</td>
<td>• The EU aims for an innovative, competitive, climate-neutral industry. Based on experiences learnt during times of the pandemic, future shortages of medicines should be prevented through a mix of policies. Policy recommendations include strengthening the production of &quot;Made in Europe&quot; medicines and increasing supply resilience.</td>
<td>Besides a mix of other policies, strengthening the production of pharmaceuticals in Europe contributes to a competitive and innovative industry.</td>
</tr>
<tr>
<td>On-going</td>
<td>European Public Health Alliance (EPHA)</td>
<td>Press Release</td>
<td>Aspects to be adopted in the pharmaceutical strategy</td>
<td>• Key aspects to be adopted in the Pharmaceutical Strategy of the EU include an extension of notification periods in case of shortages, safety stock obligations, transparency as well as shortage management plans. The EPHA suggests diversifying production sources of medicines over rehousing of production.</td>
<td>Several aspects need to be adopted in the Pharmaceutical Strategy of the EU to decrease and prevent shortages.</td>
</tr>
<tr>
<td>2021</td>
<td>European Commission</td>
<td>European Commission</td>
<td>Ensuring supply during crisis</td>
<td>• During times of crisis (Covid-19), the Commission demanded an increase in medicine production to ensure supply.</td>
<td>Strengthening the production of medicines was an important step.</td>
</tr>
</tbody>
</table>


130 European Public Health Alliance, 2022, Why patients cannot access to medicines they need in Europe, available at: [https://epha.org/why-patients-cannot-access-to-medicines-they-need-in-europe].

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<th>Date</th>
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<th>Conclusion</th>
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</thead>
<tbody>
<tr>
<td>May, 2021</td>
<td>European Commission, Directorate-General for Communication</td>
<td>Team Europe132</td>
<td>Local production in Africa</td>
<td>• Production should be <strong>strengthened</strong> through monitoring, information sharing, reporting, joint efforts of industries and demand of procurement initiatives and support.</td>
<td>Team Europe plans to make investments into the African medicine production to strengthen their healthcare system.</td>
</tr>
</tbody>
</table>
| 2020      | European Commission, Directorate-General for Health and Food Safety, European Parliament | European Commission, Montserrat, D. 133 | Pharmaceutical Strategy for Europe | **Aims:**  
  - To **strengthen supply chains** in Europe and increase the competitiveness of the market  
  - To invest in the development, research and **manufacturing** in for antibiotics due to the high rise in antimicrobial resistance  
  - To ensure **cooperation with other countries** for public procurement or joint pricing mechanisms  
  - To **tailor and review incentives** for the stimulation of innovation for critical medicines and increase of transparency and competition  
  - To **ensure supply and avoid shortages** (which are caused by parallel trade, scarce APIs, marketing strategies, weak obligations for public service or issues with reimbursement strategies). Strategies include fostering European production, joint procurement and supply diversification.  
  - To **strengthen dialogue** with stakeholders in manufacturing to understand supply chains and identify drivers for vulnerabilities (e.g. dependencies). The result of the dialogue should be tailored policy options to strengthen secure supply and increase transparency.  
  - To **cooperate with WTO members** on the trade and supply of essential medicines  
  - To **analyze new methods for manufacturing** (e.g. continuous or decentralized manufacturing)  
  - To foster environmentally-friendly, **sustainable production**  
**Additional recommendations:**  
  - To promote the production of **biosimilars and generics**  
  - To ensure an agile and stable **regulatory system**  
  - To increase and support **public-private partnerships** and ensure monitoring of supply  
  - To **incentivize European production**, adapt prices of medicines and improve coordination of health strategies at the national level.  
  - To keep the **European intellectual property system** and support its maintenance  
|           |                                                                               |                                  |                       |                                                                                                                                                                                                                                                                  |                                                                                                                                                               |

Source: Authors’ own elaboration.

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### Table 11: Documents prepared by supranational organisations or at national level

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<tr>
<th>Date</th>
<th>Commissioner</th>
<th>Author(s)</th>
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</table>
| 2022 | OECD | Chapman, S., Dedet, G., & Lopert, R. | Medicine shortages | • Between 2017 and 2019, shortage notification increased by 60% in 14 OECD countries.  
• The concentration of manufacturers in solely one area may present a big risk of vulnerability especially in times of crisis.  
• In 2019, API manufacturers were located in the US (28%), the EU (26%), China (13%), India (18%) and Canada (2%).  
| Minimizing the high concentration of manufacturing sites in single areas may reduce vulnerability. |
| 2020 | OECD | OECD | Global supply chains and Covid-19 | • Global supply chains can cause disruptions (international production etc.), but also help countries and companies recover more quickly.  
• Sourcing strategies are impacted by level of acceptable risk.  
• Recommendations include strengthening risk management and assessment, transparency and agility as well as information sharing and stronger governance.  
| The pandemic has highlighted advantages and disadvantages of global supply chains. Risk management plays an important role in future preparedness. |
| 2011 | WHO Secretariat on Public Health, Innovation and Intellectual Property | WHO | Pharmaceutical production in low- and middle-income countries | • To support local production, a number of criteria are relevant, including type of technology transfer, technical and economic value, level of development of partners etc.  
• Joint ventures are common for technology transfers.  
• Important stakeholders for local production include facilitators (e.g. research, funding, advising), government actors, multilateral organizations.  
• Technology transfer in the initiatives found in the study targeted mostly formulation, followed by API and packaging.  
• Most initiatives on API production targeted HIV/AIDS, malaria, TB and pandemic flu.  
• Depending on the aim, time to establish local production varies significantly.  
• Price, supply security, sustainability or mastery of transferred technology are examples of indicators for the success of local production.  
| Success of local production, defined through better access to medicines, is highly dependent on the context, time span and product. |
| 2011 | European Parliament | WHO | Local production in developing countries | • Governments in developing countries support local production of pharmaceuticals in order to balance supply and demand and ensure access to medicines.  
• Local production in developing countries is indeed increasing through national and international support.  
• However, there is no clear evidence that the results of local production are access to medicines.  
| Even though it is important that local production of medicines in developing countries is increasing, there is no clear evidence that it ensures access to medicines. |
| 2009 | World Bank | Bumpas, J. & Betsch, E. | API Production in developing countries | • APIs are usually bought on the open market and most companies, even though they produce both APIs and final formulations, will sell APIs on these markets.  
• Manufacturers specialize their manufacturing on the base of skills and market opportunities.  
| The API market is influenced by several factors (including price, transparency etc.), which further determine whether manufacturers enter, stay in or leave the market. |


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</table>
| 2017 | ProGenerika  | Berger, R. | Production of antibiotics in Europe | • The allocation of regulatory agencies depends on geographic location and the financial source of the manufacturer. Thus, API manufacturing in developing countries such as Africa are usually less strictly regulated.  
  • Challenges for manufacturers include lack of market transparency and inequality of access to APIs.  
  • Policy recommendations include strengthening regulatory capacities for APIs and increasing market transparency. | A relocation of API production to the EU requires political measures with the aim to change the current conditions (price, capacity, etc.). |
|      |              | 139       |            |         |            |
|      |              | Link      |            |         |            |
| 2018 |              | Berger, R. | Production of antibiotic APIs in Europe | • Current drivers for API production in non-EU countries: cost advantage, expansion and efficiency of capacities for production.  
  • 80% of APIs and intermediates are imported from non-EU countries.  
  • Example Amoxicillin: highest demanded antibiotic in Germany, dependent on a few manufacturers outside of the EU.  
  • Supply shortages of antibiotics can be the results of dependency on imports.  
  • Key barriers for the relocation of production to the EU entail high production costs, requirement of multiple production sites (one API per site for safety reasons) and low price levels for antibiotics in the EU.  
  • Possible effects of relocation include reduction of dependence, improved supply, preservation of capacity for production, market reinforcement, value for economy, export of APIs.  
  • Starting points for the relocation:  
    o Government: facilities for production, increase prices, promote relocation  
    o Industry: increase regional awareness  
    o Supply alliances: reduce cost-orientation  
    o Insurers: Change tender procedures | Production capacities in Germany could be reconstructed through governmental support with the aim to reduce dependency on non-EU countries. |
|      |              | 140       |            |         |            |
|      |              | Link      |            |         |            |


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<th>Conclusion</th>
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</table>
| 2017       | WHO, European Commission | WHO141          | Local API production in India                | • India has an extensive internal market. Therefore, reaching economies of scale was possible before entering other export markets.  
• One advantage is their local sourcing of inexpensive APIs and their efficient production. Followed by a growth in equipment and services, a cost-effective ecosystem was the result.  
• Challenges:  
  o China as a competitor (focus more on sole APIs, India more on finished pharmaceutical products) and their dependency on imports from China  
  o Increasing concern about quality of products from Indian SMEs  
  o Even though India aims to develop new drugs, there are challenges as they are not as strongly capitalized as other multinational originators.  
• Successful local manufacturing of APIs is not directly correlated to improved access to medicines, which is also proven by the Indian example.  
• An important policy in India are economic zones, which specifically enable a common use of the required infrastructure.  
• Despite the success over the last few years in API production, India faces some challenges such as their competitor China. Nevertheless, through their policies implemented, they are still a strong producer of APIs.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 2017       | WHO, European Commission | WHO142          | Local API production in China                | • In the beginning of local production, government incentivized for instance industrial zones, which facilitated infrastructure development at lower cost.  
• 97% of manufactured drugs in China are generics.  
• Due to the quick development of the industry, the medicines regulatory framework in China did not develop as quickly and properly. Hence, several SMEs cannot comply with the newly established rules and have to close.  
• Another challenge are environmental concerns in China. A possible solution for this is the establishment of industrial zones, which can commonly use for waste disposal.  
• China’s pharmaceutical industry is hard to compare to other countries due to their political system with state control etc.  
• However, some recommendations include:  
  o Linking policies in pharmaceutical industry to access to medicines locally  
  o Establishing a strong framework  
  o Environmental controls  
  o Financial, tax and related incentives  
  o Promotion of local advantage (e.g. TCM in China) for production and export  
• China also faces some challenges in their local production (including their regulatory framework), however, they are successful at establishing internal systems such as industry zones.  
Encouraging local production of medicines in Africa is possible through strong leadership and implementing incentives for local companies. |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 2017       | WHO           | Dong, J. & Mirza, Z. 143 | Local production in Africa                | • Local production contributes to reliable access to medicines that are affordable for the long term.  
• Africa is the world’s second fastest growing market for pharmaceutical production in 2016.  
• Incentives are used to increase local pharmaceutical companies. These include public procurement, non-fiscal facilitations, infrastructure development or soft loans.  
• Encouraging local production of medicines in Africa is possible through strong leadership and implementing incentives for local companies. |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 2021       | Member States of the EU and others | WHO144          | Strengthening local production of medicines | • Approaches for establishing local production are very diverse.  
• Request to Member States: strengthen leadership, develop policies, engage in networks and development organizations | Member States and the WHO shall strengthen their approaches to establish and improve local production.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

141 World Health Organization, 2017, India policies to promote local production of pharmaceutical products and protect public health, available at: https://apps.who.int/iris/handle/10665/336750.  
143 Dong and Mirza, 2016, Supporting the production of pharmaceuticals in Africa, available at: https://apps.who.int/iris/bitstream/handle/10665/271829/PMC4709802.pdf?sequence=1&isAllowed=y.  
Potential measures to facilitate the productions of active pharmaceutical ingredients (APIs)

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<th>Date</th>
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<th>Author(s)</th>
<th>Main theme</th>
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<th>Conclusion</th>
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</thead>
</table>
| 2021   | US government | The White House Washington | Strengthening supply chains and manufacturing in America | • **Complex** production mechanisms, **distribution paradigms** as well as **multinational** production sites impact the resilience of API supply.  
• Domestic production is often **not viable** due to higher costs.  
• **Solutions** for strengthening local supply chains include:  
  o Improving **transparency** of market and incentives  
  o Improving **economic stability**, including predictability provision, flexible contracts, diversification of supply  
  o Boosting **production** in the US through incentives, improved data collection, transparency, regulations and R&D  
  o Increasing **emergency capacity**  
  o Promotion of **international cooperation** to secure the supply chains | A blend of investments and financial incentives is essential to securing supply chains and fostering domestic production. |

**Source:** Authors’ own elaboration.

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### Table 12: Documents from industry and their associations (excerpt)

<table>
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<th>Date</th>
<th>Author(s)</th>
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</table>
| 2021   | Confederation of the Indian Industry and KPMG147                           | API Industry in India                            | • India imports around 68% of APIs from China. Dependency occurs especially for antibiotics such as Penicillin.  
• China’s advantages compared to India include lower costs (electricity, access to capital, logistics, set-up costs), scale of operations, policy support and availability of raw materials.  
• Policy measures to be integrated:  
  o Establishing a single window clearance system  
  o Create chemical and pharma clusters with common infrastructure to foster participation of the private sector  
  o Improved collaboration between academia and industry  
• Incentives and subsidies for establishing better technology | China has several advantages compared to India’s API production. However, India integrates policy measures to strengthen the industry again. |
| 2018   | Cogan, D., Karrar, K. & Iyer, KJ. (Access to medicines foundation)148        | Shortages of antibiotics                         | • Supply chains for antibiotics are very fragmented and complex, as many (or very few) stakeholders are involved throughout the stages of production. This makes the supply chains highly fragile and cannot properly adapt to changes in demand.  
• Priority actions for pharmaceutical companies include better demand planning (collecting and sharing data), ensure uninterrupted supply (including local production or transfer of technologies), and strengthening of distribution.  
• Ensuring supply entails the diversification of suppliers, global pooled-procurement systems as well as local production and transfer of technology and knowledge to other countries.  
• Recommendations:  
  o Pharmaceutical companies shall improve their agilities and strengthen their communication for their stock management  
  o Increase collaboration between suppliers, governments and all stakeholders  
  o Develop incentives for pharmaceutical companies | The supply chains for antibiotics (including API production) are highly complex. Therefore, solutions must be diverse and collaboration at the government and industry level is essential. |
| 2022   | European Federation of Pharmaceutical Industries and Associations (EFPIA)149 | Pharmaceutical Industry in Europe               | • In 2021, the same number of new APIs originated from China and Europe for the first time. This confirms the quick development of China’s market.  
• From 2016-2021, markets in Brazil, India and China grew by 11.7%, 11.9% and 6.7%. In comparison, the European top 5 markets grew by 5.8% on average.  
• Europe is still an important producer and research market for high-tech pharmaceuticals, including for HIV/AIDS, cancer or Multiple Sclerosis. | While the European market is an important investor and producer of high-tech drugs, Brazil, China and India are leading countries in the production of APIs with rapid market growth in the past years. |

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147 Confederation of Indian Industry and KPMG, 2020, *Indian API Industry – Reaching the Full Potential*, available at: [https://www.cii.in/PublicationDetail.aspx?enc=swL3yNIPL0AuvtDG0s5N7Hzj1d8Hk0p4TdExqCTC166m91tMrdHrJzqCzWq7n+yL8xOJIVxgwEnh4aJf49c9c3RXh15UCLo+HJf0oqSmoqV8BDVKtedM9mOAkULAc1cy+79C1K5oksxAZMbaxU+txNBGmUuZq+TF2aU6KEk=](https://www.cii.in/PublicationDetail.aspx?enc=swL3yNIPL0AuvtDG0s5N7Hzj1d8Hk0p4TdExqCTC166m91tMrdHrJzqCzWq7n+yL8xOJIVxgwEnh4aJf49c9c3RXh15UCLo+HJf0oqSmoqV8BDVKtedM9mOAkULAc1cy+79C1K5oksxAZMbaxU+txNBGmUuZq+TF2aU6KEk=).


### Potential measures to facilitate the productions of active pharmaceutical ingredients (APIs)

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<th>Date</th>
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<th>Conclusion</th>
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</thead>
</table>
| 2020        | Medicines for Europe [150]     | Medicine production in Europe | **Recommendations** for a sustainable supply chain for APIs in Europe:  
• Changes in tender policies and pricing models in order to avoid solely opting for the lowest price  
• Use digitalization for information transfers in case of shortages  
• Upgrades for the IP framework  
• Platform for European cooperation and exchange for policy reforms  | Policy action through the pharmaceutical strategy is needed to secure supply and prevent shortages in Europe. |
| 2021        | Medicines for Europe [151]     | API production in Europe     | • 84% of patients want more local production.  
• Policy recommendations include reforms in pricing and reimbursement, incentives for manufacturers, enhance regulatory efficiency, impact assessments for future policies and partnerships with the US. | The EU’s policies should play an important role in facilitating sustainable API production.            |
| 2020        | MundiCare [152]                | Global API production        | • For more than 50% of APIs globally, there are very few manufacturers.  
• Main reasons for loss of position as market in Europe: costs pressure and strict regulations.  
• The focus of European manufacturers is put on more complex APIs.  
• There is potential for European API production (arguments include technical know-how, available capacities) | Even though Europe has lost its position as API manufacturer to China and India, there is potential to increase production in Europe again. |

**Source:** Authors' own elaboration.

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Table 13: Other documents (mainly studies)

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<th>Main theme</th>
<th>Content</th>
<th>Conclusion</th>
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</table>
| 2022 | Barbieri et al. | Reshoring | • The pandemic has emphasized dependency on countries such as China due to the offshoring of production in the past decade.  
• A reshaping of supply chains is expected to happen at the political and the firm-level in the long term.  
• Existing tools for risk management in order to evaluate decision for reshoring, such as decision trees or 'Monte Carlo risk analysis approach' can be used.  
• Joint initiatives for reshoring can be an effective way as shown through activities during Covid.  
• Activities that are put in place for the short term will predominantly help coping with current transitory conditions but will adapt to the new normality. | The future of reshoring and therefore, the change in supply chains, will depend on action at the political and the company level for the long term. |
| 2019 | Beck et al. | Medicine shortages | • Policy responses are dependent on two aspects: the significance attributed to shortages by the government, and the level, on which governmental institutions discuss the problem.  
• Policy responses differ in the time frame, strategic approach and level of action taken by the government.  
• While governments in Ireland and Spain take a rather reactive approach with a focus on certain products, Austria and Germany have a more proactive approach on the prevention of shortages, focusing on APIs. The US government is drawn to mitigation policies, taken into account the therapeutic level of medicines. | Policy responses regarding medicine shortages are dependent on the significance and way the topic is perceived in governments. |
| 2020 | Berrer et al. | Pharmaceutical market in Austria | • Higher efforts in research and development through governmental action are required due to the declining number of patent applications over the last years in Austria.  
• In Austria, approximately 60% of APIs are imported.  
• The reshoring strategy for reducing import dependency should also go hand in hand with a substantial improvement in the supply situation for pharmaceutical products.  
• A crisis-proof European regulatory framework is needed to ensure that supply relationships are maintained in the EU internal market.  
• Recommendations  
  o Facilitate access to do clinical trials  
  o Close cooperation with existing companies in the field  
  o Re-design the internal supply chain  
  o EU-level: free trade agreements, Austrian level: direct investments in other countries | At the Austrian and EU-level, combined policies are required to decrease import dependency for pharmaceuticals. |
| 2015 | Bogaert et al. | Medicine shortages in France, Belgium and the EU | • Interviews found three main determinants for medicine shortages: problems in supply and distribution, manufacturing as well as economic issues.  
• Economic problems are, however, often the main issue for countries.  
• There is a need for a better coordination and cooperation at the EU level, as Member States mostly act on their own. | Cooperation at the EU level may contribute to a better management of medicine shortages. |

### Potential measures to facilitate the productions of active pharmaceutical ingredients (APIs)

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<th>Author(s)</th>
<th>Main theme</th>
<th>Content</th>
<th>Conclusion</th>
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| 2021 | Cherian et al. [157] | API production in India | • India’s dependency on imports from China for some live-saving medicines are 80-100%, for fermentation-based APIs 100%.  
• Policy recommendations for India:  
  o Short-term e.g. assessment of production viability regarding critical medicines, develop monitoring and data collecting systems, revive pharma units  
  o Mid-and long term e.g. diversify suppliers, establish production facilities, modify regulations, fiscal interventions, develop new business model (innovation) | Policy measures in India to reduce import dependency from China requires a mix of policy measures. |
| 2021 | Francas [158] | Global API supply chains | • The Chinese provinces Zhejiang, Jiangsu, and Shandong produce more than half of APIs on the market.  
• Literature finds increased quality risks in offshored pharmaceuticals  
• Restoring is highly cost-intensive and time-intensive. It would be reasonable for some critical products, but tax incentives or subsidies for reshoring are necessary.  
• Other possibilities might be applying a mix of mitigation measures or diversification of suppliers. | Reshoring API production is possible but is cost- and time-intensive and requires high investments from governments. |
| 2021 | Görg and Mösle [159] | Global API supply chains | • Diversification of suppliers reduces the risk of being affected by idiosyncratic shocks (e.g. political uncertainties) and increases stability.  
• A relocation of Cephalosporine to Europe would create 78 million Euros in additional costs (5 times more than current production in China).  
• Policy options: subventions (e.g. provision of production capacity), focusing on relocating critical medicines, restructuring of discount contracts, modification of existing tendering arrangements, increased prices for generics | Strong regulatory framework conditions must be ensured to reduce import dependency and increase relocation. |
| 2021 | Grumiller et al. [160] | Global and regional supply chains | • Import dependency, substitution, diversification in regions, diversification complexity are drivers for vulnerability of supply chains.  
• Vulnerabilities for generics are more likely to occur as the production - in particular of low-complexity, high volume APIs - of many has been outsourced.  
• A mix of following policies is recommended:  
  o Incentives for reshoring of production (especially for critical pharmaceuticals)  
  o Increasing stockpiling for high durability products  
  o Regulatory changes (diversification of suppliers)  
  o Public procurement  
  o Creating industrial commons | Generics are more vulnerable to shortages as they are mainly outsourced. Regulatory changes play a major role in securing shortages. |
| 2021 | Guinea and Espés [161] | Dependency on foreign suppliers of pharmaceutical products | • 51% of EU pharmaceutical products consumed in the EU are manufactured domestically and 53% of consumption is imported from Europe  
• EU resilience has increased between 2010 and 2019, but China became a more important supplier to the EU | Support companies to diversify global supply chains and put more focus on security of supply in procurement. |


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<th>Date</th>
<th>Author(s)</th>
<th>Main theme</th>
<th>Content</th>
<th>Conclusion</th>
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<td>2017</td>
<td>Heiskanen et al.¹⁶²</td>
<td>Medicine shortages in Finland</td>
<td>• 30 interviews in Finland were conducted with key players of the pharmaceutical market focusing on medicine shortages in the country.。&lt;br&gt;• Reasons behind shortages specifically in Finland concern the small size and volume of the Finnish pharmaceutical market and the lack of operating manufacturers, the dependency on foreign manufacturers as well as long delivery times.&lt;br&gt;• Production-related issues, including API shortages or supply chains, were considered global issues.&lt;br&gt;• On the demand side, high fluctuations play an impacting role on shortages.&lt;br&gt;• Generally, the market (un)attractiveness contributes to shortages.</td>
<td>Reasons for medicine shortages in Finland in particular are diverse and complex. However, some of them are global issues, specifically on the supply side.</td>
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<tr>
<td>2023</td>
<td>Marrone et al.¹⁶³</td>
<td>Nationalization of pharmaceutical supply chains</td>
<td>• To make the decision whether local API production is reasonable, a variety of criteria is necessary for stakeholders. It includes economic aspects on the demand (affordability, value assessment etc.) and supply side (industry competition, manufacturing costs, availability of materials), environmental influence (risk, emissions etc.), strategic vision (guarantee for access, incentives for innovation) and technical feasibility (complexity of manufacturing, quality of products).&lt;br&gt;• For addressing public health needs, a multicriteria decision-making strategy is necessary.</td>
<td>The decision on whether to nationalize production of APIs requires a multicriteria decision-making approach to meet public health needs.</td>
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<td>2021</td>
<td>Raza et al.¹⁶⁴</td>
<td>Securing supply of essential medicines</td>
<td>• Securing supply often creates a conflict between the aim to secure supply and cost-efficient production of medicines. This conflict increases the more extensive the state intervention in entrepreneurial freedom is.&lt;br&gt;• Instruments for the promotion of strengthening local production entail the subsidization of reserve capacity in local enterprises, the use of public shareholdings to reduce the migration of production capacity and to develop minimum local production capacities.&lt;br&gt;• Disadvantages of local production include higher costs for consumers and manufacturers and the need for investment and subsidies.</td>
<td>Local production is a way to secure supply of medicines, where investments in the long term are necessary.</td>
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<td>2022</td>
<td>Roehr¹⁶⁵</td>
<td>Post-Covid supply chain in the US</td>
<td>• Company Civica Rx: formed to address problems with shortages and quality control. They encourage their members to purchase in bulk for 5 years ahead to ensure profit for manufacturing.&lt;br&gt;• Company Phlow Corp: API production in Virginia through continuous flow production technique (=producing every step at the same production site).&lt;br&gt;• Impacting factors for the reshoring of production to the US will be time, cooperation (insurers – consumers, government) and competition.</td>
<td>Examples for API production in the US, using bulk purchases and the continuous flow production technique, show successful ways to reshore production.</td>
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<tr>
<td>2021</td>
<td>Sanchez and Muzzio¹⁶⁶</td>
<td>Reshoring pharmaceutical production in the US</td>
<td>• Risks for offshoring: commerce disruptions, business risks, geopolitical situations, brand damage etc.&lt;br&gt;• It is necessary to consider technological innovation to build a strategy for reshoring.&lt;br&gt;• Two methods for expanding local production quickly for final dosage manufacturing are continuous manufacturing and process analytical technologies.&lt;br&gt;• Emerging methods for pre-conditioning APIs to make them more manufacturable are radically expanding the range of applications of continuous direct compression.&lt;br&gt;• Additional experience in technologies (e.g. continuous flow synthesis and purification) is necessary. One promising technology is the SRI AutoSyn multistep flow synthesis system.</td>
<td>Access to knowledge and expertise are main drivers for successful reshoring.</td>
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¹⁶² Heiskanen et al., 2017, The reasons behind medicine shortages from the perspective of pharmaceutical companies and pharmaceutical wholesalers in Finland, available at: [https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0179479](https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0179479).
¹⁶⁵ Roehr, 2020, Bringing drug production home: how the US is rebuilding the drug supply chain after covid-19, available at: [https://www.bmj.com/content/bmj/370/bmj.m3393.full.pdf](https://www.bmj.com/content/bmj/370/bmj.m3393.full.pdf).
### Potential measures to facilitate the productions of active pharmaceutical ingredients (APIs)

<table>
<thead>
<tr>
<th>Date</th>
<th>Author(s)</th>
<th>Main theme</th>
<th>Content</th>
<th>Conclusion</th>
</tr>
</thead>
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| 2021 | Stefano et al. | Post-Covid value chains | • The pandemic confirmed the idea of **primacy of politics over economics.**  
• **US strategy** to revive production: tax rate reduction, infrastructure investments, creation of production universities and hubs, reduced energy costs.  
• **Barriers** for reshoring: high personnel cost, neglecting subsidies for innovation, wrong communication tools, not addressing specific industry, neglecting personnel education.  
• **Policies France implemented in 2020** to encourage reshoring: incentives for specific products (including drugs), tax reduction for SMEs, incentives for industrial investment, administrative support and new production plants.  
• Reshoring requires a **wide range of activities** on different levels.  
• At the supranational level, **near-shoring** of the regional value chain through a **macroregional industrial policy** is relevant.  
• Two policy recommendations:  
  - Geographic horizon: near- or back-shoring  
  - Enlargement of re-shoring target: single companies or value chains | Policies for relocation should be combined with other policies in the industry which enforce competitiveness in a broad geographical scope (home country or macro-region) to ensure product value and decreased production costs. |

Source: Authors' own elaboration.

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European countries have been experiencing medicine shortages due to disruptions in the supply chain. Reshoring the productions of active pharmaceutical ingredients (APIs) is considered as an approach to secure the supply. This in-depth analysis informs about the current API production in the European Union, including reshoring initiatives. Studying potential benefits and challenges of local API production and the processes of reshoring, the document explores measures to facilitate the production of APIs in the European Union.

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