



## COUNTRY PROFILE: CANCER MEDICINES SHORTAGES

# GERMANY

### Introduction

EIU indicators	2018 ratings
Political environment rating (10=high)	8.7
Effectiveness of system in policy implementation (5=high)	4.0
Infrastructure rating (10=good)	7.6
Level of corruption (5=low)	4.0

Germany has the highest expenditure on health (11.2%) as a share of its Gross Domestic Product (GDP) in the European Union (EU), and the second highest in terms of health spending per capita (EUR 3,996).<sup>1</sup> Most of the funding for health comes from the public sector, accounting for 84.5% of total health expenditure in 2015. With the oldest social health insurance system in the world, 99.9% of the German population is covered by health insurance.<sup>1</sup>

In 2016, Germany's pharmaceutical expenditure per capita as a share of the total health expenditure was the highest in the EU.<sup>2</sup> The country is the biggest pharmaceuticals producer in the EU and the fourth largest pharmaceutical market globally, with 13.5% of market share.<sup>3</sup> In the past decade the continuous increases in pharmaceutical expenditure have been a challenge for the sustainability of the health system.<sup>4</sup> To address this issue, in 2011, the German government introduced a new legislation, 'Act on the Reform of the Market for Medicinal Products (AMNOG)', regulating the assessment and pricing of new medicines.<sup>2</sup> Meanwhile, the constant pricing pressure on older, inexpensive, generic medicines has reduced the number of manufacturers of these medicines, contributing to medicines shortages.<sup>5</sup> According to the definition of the European Medicines Agency (EMA), a medicine shortage "occurs when supply cannot meet demand at a national level."<sup>6</sup>

The 2018 European Association of Hospital Pharmacists (EAHP) survey reported that 97% of German pharmacists experienced shortages on a weekly or even daily basis, with 78% responding that this had a negative impact on patient care.<sup>7</sup> The medicines most often affected by shortages included antimicrobials (91%), anaesthetics (69%) and oncology medicines (57%).<sup>7</sup> These results were also confirmed by the 2018 Drug Commission of German Pharmacists (AMK) survey, which explored medicines shortages in the context of patient safety and reported that almost 90% of community pharmacists and over 80% of hospital pharmacists were affected by shortages of different types of medicines including cancer medicines.<sup>5</sup>

The impact of shortages on patient safety and outcomes is particularly relevant for cancer patients. Cancer is the second leading cause of death in Germany after cardiovascular diseases. In 2014, it accounted for 29% of deaths in men and 23% of deaths in women, with 10% of the total deaths from lung, colorectal and breast cancer.<sup>1</sup> Given the cancer burden in Germany, cancer medicines shortages are a big concern.

### What is happening on the ground?

Over the past few years, with the growing collection of data on the magnitude of medicines shortages in Germany, awareness about the issue has increased among policymakers, health professionals and

other stakeholders.<sup>5,8,9</sup> In 2013, the Federal Institute for Drugs and Medical Devices (BfArM) launched a reporting system for shortages, an online platform providing information based on notifications from marketing authorisation holders (MAHs). On 20 January 2019, the BfArM platform listed 358 shortage notifications, 37 of which were for cancer medicines (Table 1). Of the latter, 76% were caused by manufacturing problems and had an average duration of 212 days.<sup>10</sup>

In 2017, the German Society for Haematology and Medical Oncology (DGHO) published a report on cancer medicines shortages.<sup>9</sup> This study reports the shortages of a number of innovative and older generic cancer medicines, including 5-fluorouracil (5-FU), cytarabine, daunoblastin, doxorubicin, etoposide phosphate, melphalan and vinorelbine, between 2012 and 2016.<sup>9</sup> The report emphasises that for “life-threatening illnesses, a supply shortage can lead to deterioration of the prognosis for patients.”<sup>9</sup> The DGHO study and the AMK survey reported that the negative consequences of shortages on patients range from changes in treatment schedules, to delays or discontinuation of treatment when no alternatives are available.<sup>5,9</sup>

**Table 1. Examples of cancer medicines affected by shortages in 2018**

Cancer Medicine	Indication
Capecitabine	Breast cancer; Colorectal cancer; Gastric cancer; other cancers
Carboplatin	Cervical cancer; Head and neck cancer; Ovarian cancer; Lung cancer
Etoposide phosphate	Testicular carcinoma; Lung cancer
Fludarabine	Chronic lymphocytic leukaemia; Non-Hodgkin’s lymphoma; Acute myeloid leukaemia
Melphalan	Multiple myeloma, stem cell transplantation (blood cancer)
Methotrexate	Acute lymphoblastic leukaemia; Head and neck cancer; Non-Hodgkin’s lymphoma; Osteosarcoma; other cancers
5-fluorouracil	Colon carcinoma; Colorectal carcinoma; other cancers

Source: Federal Institute for Drugs and Medical Devices (BfArM), 20 January 2019<sup>10</sup>

Our primary research confirms that the situation in the country is improving. In fact, the potential shortage of daunorubicin, an essential medicine for the treatment of acute myeloid leukaemia (AML), that was announced in March 2019 never occurred.<sup>10</sup> Most of the time pharmacists manage to find alternative solutions and as a result shortages rarely affect patients’ treatment.

**Why do inexpensive cancer medicines go missing?**

The DGHO differentiates two types of availability issues:

- *Delivery bottlenecks*, which refer to a situation where a medicine is not immediately available or is not available in the required volumes. These problems are usually resolved by pharmacists, although it can be a time-consuming task to identify an alternative medicine with the same active substance.

- *Supply bottlenecks or shortages*, which occur when there is no equivalent medicine approved in Germany, or when no other manufacturer exists. This type of shortage can have a negative impact on patients.<sup>9</sup>

The DGHO report describes five main causes for shortages: manufacturing problems, distribution in the global market, increase in demand, pricing, and market withdrawals.<sup>9</sup>

### **Case study: Melphalan<sup>5,9</sup>**

Melphalan is a medicine used to treat different types of cancers, such as multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, and sarcoma. When used in stem cell transplantation in young people, melphalan plays a crucial role for survival. In 2015 and 2016, melphalan was affected by several shortages due to Good Manufacturing Practice (GMP) problems. As melphalan was produced by a single European manufacturing facility in Italy, production problems affected several countries in Europe. Scheduled treatments were delayed and after the production resumed, hospitals could only order the medicine for patients with acute need.<sup>9</sup> As a result of the shortage, the procedure for autologous stem cell transplantation had to be changed in 15 patients, and for 48 patients the transplantation had to be postponed.

**Manufacturing problems:** Most of the cancer medicines shortages in Germany are related to manufacturing issues.<sup>9-11</sup> These are the result of non-compliance with quality standards, a complex production process, issues with active substances, or when there is a small number of manufacturers. A number of older cancer medicines, such as etoposide or vincristine, are dependent on naturally occurring active substance which makes them vulnerable to shortages.<sup>9</sup>

**Low prices:** When the prices of some older, essential medicines become too low, distributing these products in Germany is no longer economically attractive for the manufacturers and they may leave the market. For example, in 2012, when most MAHs withdrew 5-fluorouracil (5-FU) from the market due to the extremely low price of 3.90 euros for one ampoule of 5-FU 50mg, the medicine went on shortage.<sup>9</sup>

**Production outsourcing:** To cope with the increasing pricing pressure, pharmaceutical companies have relocated and concentrated the production in countries, such as India and China, where the costs of production are lower. However, this approach increases the potential risk for and the impact of shortages.

**Demand fluctuations:** Although relatively rare, shortages can occur as a result of an unexpected increase in the demand. For example, when 5-FU was on shortage, the demand for capecitabine, a substitute for 5-FU, increased leading to a shortage.<sup>9</sup>

Various stakeholders reported in the past that the BfArM list of medicines shortages was not comprehensive as it relies on voluntary notifications of shortages by MAHs.<sup>5,10</sup> Moreover, pharmacists expressed the concern that shortages might be underreported, partly because the BfArM defines a medicine shortage as "an interruption in the normal volume of supply lasting more than two weeks."<sup>5</sup> Pharmacists also reported that they preferred to receive information about shortages directly from manufacturers, from wholesalers, or from the pharmaceutical press rather than from the BfArM.<sup>5</sup> To overcome these issues, clearer information needs to be communicated to all stakeholders in Germany.

**Table 2. Who is involved in tackling shortages in Germany and what are the current initiatives?**

Competent Authority	Responsibilities and current initiatives
Federal Institute for Drugs and Medical Devices (BfArM) <sup>10</sup>	<ul style="list-style-type: none"> <li>• Receives and manages notifications for shortages or withdrawals of medicines from marketing authorisation holders (MAH).</li> <li>• Evaluates the extent of shortages and communicates with the stakeholders affected.</li> <li>• Manages and updates the online public platform for shortages.</li> <li>• Publishes additional information for alternative treatments provided by medical societies, when the shortage can cause problems for patient treatment.</li> </ul>
Paul Ehrlich Institute (PEI) <sup>12</sup>	<ul style="list-style-type: none"> <li>• Responsible for monitoring shortages related to human vaccines.</li> <li>• Disseminates information about vaccines shortages.</li> </ul>
Jour Fixe, permanent commission on medicines shortages <sup>9</sup>	<ul style="list-style-type: none"> <li>• Involves stakeholders from different sectors, such as the federal government, medical societies, pharmacists, and the pharmaceutical industry.</li> <li>• Discusses prevention and management of shortages.</li> <li>• Provides recommendations for action.</li> <li>• Develops a list of active ingredients considered to be subject of supply shortages.</li> </ul>

A number of feasible solutions mostly based on best practice examples, such as the FDA shortages initiatives, and the EMA guidance about shortages related to manufacturing and quality issues, were also proposed in the DGHO report.<sup>9, 13-15</sup> The proposed measures included: 1) Mandatory notification of shortages by manufacturers, monitored by the BfArM; 2) Protection of essential medicines by stockpiling the supply for 3-6 months; limiting discount negotiations for certain essential medicines and creating incentives for MAHs to keep low-priced medicines on the market; 3) Facilitate medicine imports; 4) Legal obligation for the continued supply of authorised medicines and fines for non-compliant MAHs; 5) Risk management; 6) Promotion of the pharmaceutical industry in Europe.<sup>9</sup>

The Jour Fixe, the German permanent commission on medicines shortages, was established in 2016 within the framework of the Federal Ministry of Health initiative, Pharma Dialogue. The Jour Fixe has the mandate to monitor the situation of medicines shortages in the country and work towards finding solutions. This group includes stakeholders from the Federal Authorities, the Drug Commission of German Pharmacists and various medical societies, currently represented by the DGHO.<sup>9</sup> The Jour Fixe has issued several recommendations on how to tackle medicines shortages which are in line with the measures proposed by the DGHO and which have been enacted in federal legislation. For example, the 2017 Act to Strengthen the Supply of Medicines in the Statutory Health Insurance (GKV-AMVSG) made the notification of shortages mandatory and introduced penalties for MAHs in case of non-compliance.<sup>16</sup> The imports of unauthorised medicines from other markets are now also allowed by law when there is no substitute for an essential medicine that is unavailable in the country. During a shortage event in 2018, an alternative medicine was immediately imported from Australia, before the supply shortage affected hospital pharmacies, showing that this measure can prevent shortages.\*

### Looking into the future

As shown above, over the past few years, several measures have been introduced to prevent and manage medicines shortages in Germany.<sup>5,9</sup> The support of healthcare professionals, policymakers and regulatory authorities, such as the Federal Ministry of Health and the BfArM, has been key to the implementation of these measures and for the amendments in the legal framework to guarantee the

\* Expert interview

supply of medicines. As Germany is the fourth largest pharmaceutical market globally, the MAHs have greater interest in collaborating with the national authorities in finding solutions for specific shortage situations, compared to other European countries with smaller pharmaceutical markets.<sup>9</sup>

- Some stakeholders still doubt whether the mandatory reporting obligations for MAHs and the “intensified monitoring by the federal authorities in Germany” could guarantee uninterrupted medicines supply in the future.<sup>5</sup> Moreover, mandatory reporting is limited to shortages affecting hospital pharmacies.
- Under the 2017 legal changes it is now possible to facilitate the import of unlicensed essential medicine, where no substitute exists. According to the law, medicines procurement is coordinated centrally, saving time and effort for individual hospitals.\*
- The obligation introduced by the GKV-AMVSG to inform hospitals about delivery problems for prescription medicines for inpatient care should help healthcare professionals to prevent the negative impacts of potential shortages of cancer medicines on patients.
- The abolition of exclusive discount contracts with only one manufacturer could help prevent shortages as reliance on a single supplier is a potential risk for shortage.

### Potential solutions

#### Solution 1

#### Extend the mandatory notification for delivery issues to outpatient clinics

- The obligation introduced by the GKV-AMVSG to inform hospital pharmacies about delivery problems with prescription medicines for inpatient care should be extended to outpatient clinics.

#### Solution 2

#### Explore different pricing strategies for inexpensive, essential cancer medicines

- Identify essential cancer medicines which may be at risk of shortages and develop pricing mechanisms that would protect the uninterrupted supply of these medicines.
- Create incentives for MAHs to keep low-priced medicines on the market.

#### Solution 3

#### Promote national or European pharmaceutical production

- Consider establishing European production sites for essential cancer medicines to prevent shortages due to manufacturing and quality issues.<sup>9</sup>

\* Expert interview

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## References

1. OECD/European Observatory on Health Systems and Policies. Germany: Country Health Profile 2017, State of Health in the EU. OECD Publishing, Paris/European Observatory on Health Systems and Policies, Brussels., 2017. Available from: <http://www.oecd.org/publications/germany-country-health-profile-2017-9789264283398-en.htm>.
2. OECD/EU. Health at a Glance: Europe 2018: State of health in the EU cycle. Paris: OECD Publishing, 2018. Available from: [https://ec.europa.eu/health/sites/health/files/state/docs/2018\\_healthatglance\\_rep\\_en.pdf](https://ec.europa.eu/health/sites/health/files/state/docs/2018_healthatglance_rep_en.pdf).
3. Germany Trade And Invest (GTAI). The pharmaceutical industry in Germany: Issue 2017/2018. Berlin: Germany Trade And Invest (GTAI), 2018. Available from: [https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=2ahUKewiX8OC6yvrgAhX1oXEKHWISCB0QFjAAegQIChAC&url=https%3A%2F%2Fwww.vfa.de%2Fdownload%2Fthe-pharmaceutical-industry-in-germany.pdf&usg=AOvVaw1gFcR2EO\\_e8TZkouN-Nkhy](https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=2ahUKewiX8OC6yvrgAhX1oXEKHWISCB0QFjAAegQIChAC&url=https%3A%2F%2Fwww.vfa.de%2Fdownload%2Fthe-pharmaceutical-industry-in-germany.pdf&usg=AOvVaw1gFcR2EO_e8TZkouN-Nkhy).
4. Voda AI, Bostan I. Public Health Care Financing and the Costs of Cancer Care: A Cross-National Analysis. *Cancers* (Basel). 2018;10(4).
5. Said A, Goebel R, Ganso M, et al. Drug shortages may compromise patient safety: Results of a survey of the reference pharmacies of the Drug Commission of German Pharmacists. *Health Policy*. 2018;122(12):1302-9.
6. EMA. Improving reporting and monitoring: EU-wide shortage definition and metrics. Multi-stakeholder meeting with the HMA/EMA Task Force on availability of authorised medicines, 9 November 2018 [Internet]. London: European Medicines Agency; [cited 10 January 2019]. Available from: [https://www.ema.europa.eu/documents/presentation/presentation-improving-reporting-monitoring-eu-wide-shortage-definition-metrics-b-cuddy-hansen\\_en.pdf](https://www.ema.europa.eu/documents/presentation/presentation-improving-reporting-monitoring-eu-wide-shortage-definition-metrics-b-cuddy-hansen_en.pdf).
7. European Association of Hospital Pharmacists (EAHP). Medicines shortages in European hospitals: Medicines shortages in German hospitals. Brussels European Association of Hospital Pharmacists, 2018. Available from: [http://www.eahp.eu/sites/default/files/germany\\_medicinesshortages.pdf](http://www.eahp.eu/sites/default/files/germany_medicinesshortages.pdf).

8. European Association of Hospital Pharmacists (EAHP). Medicines shortages in European hospitals. Brussels: European Association of Hospital Pharmacists, 2018. Available from: [http://www.eahp.eu/sites/default/files/report\\_medicines\\_shortages2018.pdf](http://www.eahp.eu/sites/default/files/report_medicines_shortages2018.pdf).

9. Wörmann B, Lüftner D. Arzneimittelengpässe am Beispiel der Hämatologie und Onkologie: Mit Übersicht zur Situation in anderen Fachgebieten Berlin: Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie e.V., 2017. Available from: [https://www.dgho.de/publikationen/schriftenreihen/anzneimittelengpaesse/dgho\\_gpsr\\_IX\\_DE\\_web\\_und%20einleger\\_170309.pdf](https://www.dgho.de/publikationen/schriftenreihen/anzneimittelengpaesse/dgho_gpsr_IX_DE_web_und%20einleger_170309.pdf).

10. Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM). Lieferengpässe für Humanarzneimittel [Internet]. Berlin: Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM); [cited 11 March 2019]. Available from: [https://www.bfarm.de/DE/Arzneimittel/Arzneimittelzulassung/Arzneimittelinformationen/Lieferengpaesse/\\_functions/Filter suche\\_Formular.html?nn=11296612](https://www.bfarm.de/DE/Arzneimittel/Arzneimittelzulassung/Arzneimittelinformationen/Lieferengpaesse/_functions/Filter suche_Formular.html?nn=11296612).

11. Pauwels K, Huys I, Casteels M, et al. Drug shortages in European countries: a trade-off between market attractiveness and cost containment? BMC Health Serv Res. 2014;14:438.

12. Paul-Ehrlich-Institut. Lieferengpässe von Human-Impfstoffen gegen Infektionskrankheiten [Internet]. Langen: Paul-Ehrlich-Institut; [updated 17 October 2018; cited 11 March 2019]. Available from: <https://www.pei.de/DE/anzneimittel/impfstoff-impfstoffe-fuer-den-menschen/lieferengpaesse/informationen-lieferengpaesse-impfstoffe-node.html>.

13. FDA. FDA Drug Shortages: Current and Resolved Drug Shortages and Discontinuations Reported to FDA [Internet]. Silver Spring, MA: U.S. Food and Drug Administration; [cited 24 February 2017]. Available from: <http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>.

14. EMA. Criteria for classification of critical medicinal products: Shortages due to GMP non-compliance/quality defects. London: European Medicines Agency, 2013. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2014/01/WC500159381.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/01/WC500159381.pdf).

15. EMA. Risk indicators for Shortages (Manufacturing and Quality). London: European Medicines Agency, 2014. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2014/01/WC500159386.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/01/WC500159386.pdf).

16. Federal Government (Ministry of Health). Act to Strengthen the Supply of Medicines (Arzneimittelversorgungsstärkungsgesetz). 2017.