Engpässe und Abrisse in der Arzneimittelversorgung: am Beispiel onkologischer Wirkstoffe – Position der AkdÄ

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AkdÄ in der Bundesärztekammer

HELIOS Klinikum Berlin-Buch

DK Gupta¹ and S-M Huang²

Every day it is easy to find news articles detailing the impact of drug shortages on patients. Where this was once only a concern of patients with rare, orphan diseases, it is now the concern of patients receiving even the most common chemotherapeutic regimens, the most efficacious antimicrobial therapy, or even the most rapid-acting analgesics, largely as a result of manufacturing quality problems. Unfortunately for many of these patients, there are no efficacious alternatives.
A medically necessary drug product is one that is used to treat or prevent a serious disease or medical condition for which there is no alternative drug, available in adequate supply, that is judged by FDA medical staff to be an adequate substitute.

Drug shortage:

The total supply of all clinically interchangeable versions of an FDA-regulated drug product is inadequate to meet the projected demand at the user level.

Drug shortages followed by FDA, by year

U.S. Shortages

2011: 267
73% Generika

1.06.2011: 178
11% „short supply“
Survey by AHA, ASHP, ISMP*:

- In all (responding) hospitals: drug shortages (2011)
- Drug shortages: delayed treatment (82% of hospitals)
- Labor costs (hospitals) to manage drug shortages: 216 mio. US-$
- **Patient impact: five deaths and numerous medication errors**

* http://www.fda.gov/Drugs/NewsEvents/ucm265968.htm
25. Mai 2013

Current Drug Shortages Index

The majority of information in this section is provided to FDA by manufacturers. Communication between FDA and the public is an essential component of preventing and mitigating drug shortages. To ensure that the information in this section is current, FDA appreciates all information and updates about shortages provided by manufacturers. We post information about shortages as soon as we receive it from the manufacturers. To report information about shortages or supply issues, manufacturers can send updates to drugshortages@fda.hhs.gov. Healthcare professionals and patients are also encouraged to notify us of shortages at drugshortages@fda.hhs.gov.

**Listed by Generic name or Active Ingredient**

<table>
<thead>
<tr>
<th>Alphabetical Order</th>
<th>Drug Name</th>
<th>Update Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Acetylcysteine Inhalation Solution</td>
<td>UPDATED 6/24/2013</td>
</tr>
<tr>
<td></td>
<td>Acetaminophen Sodium Injection</td>
<td>initial posting 11/19/2012</td>
</tr>
<tr>
<td></td>
<td>Aflatoxin (Aflataxin) Injection</td>
<td>initial posting 1/23/2012</td>
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<tr>
<td></td>
<td>Alfentanil (Alfenta) Injection</td>
<td>initial posting 1/29/2012</td>
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<tr>
<td></td>
<td>Allopurinol (Coralith) Injection</td>
<td>initial posting 1/27/2012</td>
</tr>
<tr>
<td></td>
<td>Aminocaproic Acid Injection</td>
<td>initial posting 2/14/2012</td>
</tr>
<tr>
<td></td>
<td>Aminophylline (Aminophylline) Injection</td>
<td>initial posting 12/19/2012</td>
</tr>
<tr>
<td></td>
<td>Aprotinin Injection</td>
<td>initial posting 3/9/2013</td>
</tr>
<tr>
<td></td>
<td>Aprotinin (Protamin) Injection</td>
<td>initial posting date 1/31/2013</td>
</tr>
<tr>
<td></td>
<td>Argatroban Injection</td>
<td>initial posting 2/11/2013</td>
</tr>
<tr>
<td></td>
<td>Atropine besylate (Atropine Injection)</td>
<td>initial posting 2/27/2012</td>
</tr>
<tr>
<td></td>
<td>Atropine Sulfate Injection</td>
<td>UPDATED 2/20/2013</td>
</tr>
</tbody>
</table>

back to top

| B                  | Bacteriostatic 0.9% Sodium Chloride Injection | initial posting 9/10/2012 |
|                    | Barium Sulfate for Suspension Injection | initial posting 10/12/2012 |
|                    | Bisulfur Eleylchyldrolchlorophyl Chloride Injection | initial posting 10/13/2012 |
|                    | Bismuth subsalicylate Injection | initial posting 3/10/2012 |
|                    | Bumatophene Injection | initial posting 9/21/2012 |
|                    | Buovacine Hydrochloride Injection | initial posting 2/22/2012 |
|                    | Buovacine Hydrochloride Injection | initial posting 2/22/2012 |

99% of HPs experience medicines shortages in past year

21 February 2013

The European Association of Hospital Pharmacists (EAHP) has published headline results of a recent survey that reveals 99% of responding hospital pharmacists say they have experienced difficulties with medicines shortages in the past year.

With over 300 respondents from 27 countries, the survey also uncovered that 63% of hospital pharmacists report medicines shortages to be a weekly, sometimes daily, occurrence. 77% consider that problem has become worse in the last year.

Announcing the results at an event in the European Parliament on access to medicines EAHP President Roberto Frontini said:

“These headline results confirm what I have increasingly heard from our members across Europe: that the shortages problem is widespread, doesn’t respect national borders, and urgently requires attention if patient care and health services are not to suffer.

Managing shortages and trying to source supply distracts pharmacists from other core tasks, places burden on support staff and can increase stress and workload in the pharmacy environment with consequent impacts on the risk of error. Substitution of medicines in case of shortage of formulary drugs can also confuse doctors and nurses, further raising risks to patient safety.

I want to take this opportunity at the European Parliament to call on all partners to work together in identifying and enacting solutions. This includes industry and supply chain actors, regulatory authorities, and all health professions involved in medicines. I also believe there is a role for the European Commission in bringing Governments and others together on this issue.”

Spain - 44 million people

![Bar chart showing number of incidents and number of medical products affected from 2007 to 2011.](image-url)
Häufige Ursachen

Rohstoffe nicht verfügbar, Qualitätsprobleme, veraltete Produktionsstätten, regulatorische Anforderungen, wenige Alternativpräparate, steigende Nachfrage, Kostendruck, ökonomische Entscheidungen

Dynamics of Sterile Injectable Drug Shortages

Factors that turn a supply disruption into a shortage.

Manufacturing Issues

- Few Producers
- Specialized Facilities
- Dedicated Lines

Supply Disruption

Contributing Factors

- Just-in-Time Inventory

Drug Shortage
The problem is exacerbated by market concentration in the generic injectable market.

Percentage of Generic Injectable Market Held by Top Manufacturers, 2001-2010

(Source: IMS Health, IMS National Sales Perspective™, Extracted August 2011.)
Market concentration in select generic sterile-injectable classes.

![Bar chart showing market share for different classes of generic sterile-injectable products.](chart)

- **All other**:
  - American Regent: 30%
  - Baxter pharm. div.: 14%
  - Hospira: 13%

- **Anti-infectives, systemic**:
  - American Regent: 34%
  - Baxter pharm. div.: 19%
  - Hospira: 13%

- **Antineoplastic agents**:
  - American Regent: 30%
  - Baxter pharm. div.: 25%
  - Hospira: 16%

- **Nutrients and supplements**:
  - American Regent: 52%
  - Baxter pharm. div.: 25%
  - Sandoz: 14%

- **Analgesics**:
  - American Regent: 75%
  - Baxter pharm. div.: 16%
  - Sandoz: 4%
The Reality of Drug Shortages — The Case of the Injectable Agent Propofol

Valerie Jensen, R.Ph., and Bob A. Rappaport, M.D.

Oktober 2009

3 Anbieter Qualitätsmängel „aus 3 wurde 1“
Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages

J Woodcock¹ and M Wosinska¹

56% Quality

9% Discontinuation

20% Delays/Capacity

Legend:
- Quality
- Delays/Capacity
- Discontinuation
- Increased Demand
- Other/Unknown
- Loss of Manufacturer Site
- Raw Materials
- Packaging Component
Drug shortages followed by FDA, by drug classes

- Oncology: 28%
- Antibiotic: 13%
- Electrolyte/Nutrition: 11%
- Hormonal: 6%
- Neuromodulator: 9%
- Drug classes with five or fewer shortages: 33%
Medication Shortages Threaten Cancer Care

The oncology community and the FDA tackle ongoing drug shortage problem
Chemotherapy Drug Shortages in the United States: Genesis and Potential Solutions

Michael P. Link, Stanford University School of Medicine, Stanford, CA
Karen Hagerty, American Society of Clinical Oncology, Alexandria, VA
Hagop M. Kantarjian, MD Anderson Cancer Center, Houston, TX

Reason

<table>
<thead>
<tr>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Increased national and worldwide demand for oncology drugs</td>
</tr>
<tr>
<td>• Shortages of supply of raw materials</td>
</tr>
<tr>
<td>• Production problems; contamination of materials</td>
</tr>
<tr>
<td>• Aging production plants</td>
</tr>
<tr>
<td>• Limited inventories of generic drugs to reduce company costs</td>
</tr>
<tr>
<td>• Limited profit margins for generic drugs; Medicare ASP + 6% reimbursement system</td>
</tr>
<tr>
<td>• Gray market, stockpiling, and price gouging</td>
</tr>
<tr>
<td>• Private oncologists favoring use of brand name over generic drugs</td>
</tr>
<tr>
<td>• FDA over-regulation and long timelines to approve new sources of generic drugs</td>
</tr>
</tbody>
</table>

Abbreviations: ASP, average sales price; FDA, US Food and Drug Administration.
For the first time in the United States, some essential chemotherapy drugs are in short supply. Most are generic drugs that have been used for years in childhood leukemia and curable cancers —

The main cause of drug shortages is economic. If manufacturers don’t make enough profit, they won’t make generic drugs.
lokoregionäre Therapie
systemische Therapie

"targeted" Therapie
"magic bullet?"

Ära der Genomforschung
The Impact of Drug Shortages on Children with Cancer —
The Example of Mechlorethamine

Monika L. Metzger, M.D., Amy Billett, M.D., and Michael P. Link, M.D.
The NEW ENGLAND JOURNAL of MEDICINE

The Impact of Drug Shortages on Children with Cancer — The Example of Mechlorethamine

Monika L. Metzger, M.D., Amy Billett, M.D., and Michael P. Link, M.D.

### Lomustine Capsules (initial posting - 5/6/2013)

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Availability and Estimated Shortage Duration</th>
<th>Related Information</th>
<th>Shortage Reason (per New Legislation-FDA SIA)*</th>
<th>Date Updated</th>
</tr>
</thead>
<tbody>
<tr>
<td>NextSource Biotechnology, LLC</td>
<td>Lomustine capsules 10 mg: 5 count/bottle NDC 58181-3030-5 (Old EMS NDC#: 0015-3030-20; 20 count/bottle)</td>
<td>Limited supply available For emergency direct or drop shipment, contact customer service 1-855-572-2468</td>
<td>Divestiture of ownership for Lomustine capsules from Bristol Myers Squibb Company (EMS) to Corden Pharma Latina S.p.A. The new distributor in US market is NextSource Biotechnology LLC: Corden Pharma Latina S.p.A./NextSource Biotechnology LLC is currently working with FDA to alleviate shortage. See Dear Healthcare Professional Letter (PDF - 113KB) for additional information on CCNSB (Lomustine capsules) and Dear Healthcare Professional Letter (PDF - 111KB) for information on Lomustine Capsules currently available.</td>
<td>Other</td>
<td>Revised 5/24/2013</td>
</tr>
</tbody>
</table>
What impact do drug and biological product shortages have on research and clinical trials? What actions can FDA take to mitigate any negative impact of shortages on research and clinical trials?

**The impact of drug shortages on cancer clinical trials**

The shortage of some cancer drugs is not just affecting patients currently undergoing standard or non-investigational treatment, but it is also having a significant negative impact on current and future cancer clinical trials. Approximately half of all active cooperative group cancer clinical trials have at least one drug on the shortages list.

Furthermore, as patients are recruited for clinical research trials with the intent to receive an investigational therapy, the treatment described in the consent form details both the benefits, side effects, and other standard of care treatment options. It is concerning that a patient who opts to receive an investigational treatment in combination with an existing drug, which is short supply, could have instead elected to receive alternative, standard treatment – perhaps in a more timely way. Treatment delays of days to months are critical in the life of a cancer patient and could limit their chances for a cure or remission of their disease.

Another residual impact of drug shortages is the delay in obtaining the data necessary to bring new cancer therapeutics to patients. With more than 400 cancer agents in various stages of development, it is imperative that cancer clinical trials continue uninterrupted in order to obtain the necessary data to seek approval of new anti-cancer drugs as soon as possible.
WEATHERING THE STORM: MANAGING THE DRUG SHORTAGE CRISIS

From the October 7, 2010 issue

All healthcare organizations have disaster plans in place that they practice and refine in preparation for an unexpected crisis. These plans are not developed "on the fly" because healthcare providers recognize the value of planning for the unexpected and the necessity of minimizing potentially life-saving interruptions in care. The ongoing problem with drug shortages in our nation is rising to the level of "disaster" status. Drug shortages continue to take an enormous toll on healthcare providers who must deal with the problem on a daily basis, and on patients who are on the receiving end of the shortages.

According to more than 1,800 respondents to our recent 2010 survey, the conditions associated with drug shortages during the past year have been the worst ever, with little hope for improvement in the near future. Respondents were most alarmed by:

- The ever-increasing volume of critically important medications in short supply
- The use of less desirable, unfamiliar alternative drugs—if available
- Errors and poor patient outcomes caused by absent or delayed treatment or preventable adverse drug events caused by the use of alternative drugs or dosage forms
- The lack of advanced warnings about impending shortages
- Precious clinical hours lost to time-consuming activities required to manage drug shortages.
Near Misses, Errors and Adverse Outcomes

Approximately one in three (35%) respondents said that their facility experienced an error that could have led to patient harm during the past year due to a drug shortage. About one in four reported errors that reached patients and one in five reported adverse patient outcomes. However, many respondents commented that errors and adverse outcomes are difficult to quantify due to factors such as voluntary reporting methods, and felt the frequency of adverse events due to drug shortages is actually much higher.

Respondents described more than 1,000 errors and adverse patient outcomes during the past year related to more than 50 drugs on the shortage list that became abruptly unavailable, often without adequate notice. Especially troubling is that most drugs involved in the shortages are high alert medications more likely to cause serious patient harm when involved in an error, such as propofol, heparin, morphine, neuromuscular blocking agents, and chemotherapy agents.
Other Difficulties Identified

During the past year, more than half of survey respondents reported *frequently* or *always* encountering every one of the following potential difficulties associated with drug shortages:

- Little or no information available about the duration of a drug shortage
- Lack of advanced warning from manufacturers and suggested alternatives
- Little or no information about the cause of the drug shortage
- Substantial resources spent investigating the shortage and developing a plan of action
- Difficulty obtaining a suitable alternative product
- Experience a significant financial impact
- Lack of a suitable alternative product
- Substantial resources spent preparing and/or administering the alternative products
- Risk of adverse patient outcomes
- Internal hoarding of medications associated with impending shortages
- Physician anger towards pharmacists/nurses/hospitals in response to a drug shortage
Recommendations:

- Increase FDA Authority
- Improve FDA Communication with Stakeholders
- Examine Impact of Current FDA Requirements on Shortages
- Develop a National Registry
- Provide Economic Incentives to Manufacturers of Critical Drugs
Drug Shortages: What Does France Do Better Than Canada?
March 2012

<table>
<thead>
<tr>
<th>Variable</th>
<th>France†</th>
<th>Canada‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of drug products in shortage</td>
<td>46.8±3.0</td>
<td>347.3±22.4</td>
</tr>
<tr>
<td>No. of manufacturers with at least one product in shortage</td>
<td>21.0±1.6</td>
<td>14.0±1.4</td>
</tr>
<tr>
<td>No. of drug products in shortage per manufacturer</td>
<td>2.2±0.1</td>
<td>19.4±11.4</td>
</tr>
<tr>
<td>No. of generic drugs in short supply</td>
<td>34.3±2.1</td>
<td>177.5±15.8</td>
</tr>
<tr>
<td>No. of shortages per generic drug</td>
<td>1.4±0.0</td>
<td>2.0±0.1</td>
</tr>
</tbody>
</table>

Frankreich im Vgl. zu Kanada:
seit 2002 präventive Maßnahmen; u.a. seit 2004
Informationspflicht der pU über potenzielle/aktuelle Lieferengpässe
**Lieferengpässe von Humanarzneimitteln**

**Erstellt:** 26.04.2013  
**Aktualisiert:** 23.05.2013


[PDF-Formular zur elektronischen Meldung von Lieferengpässen an das BfArM (Version 0.5) (Größe: 603 KB)]

**Wichtige Hinweise zur nachfolgenden Liste**


<table>
<thead>
<tr>
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<tr>
<td>Certoparin-Natrium</td>
<td>1302</td>
<td>Mono-Embolox multi 3000 I.E./0,5 ml Injektionslösung (PZN 06187761)</td>
<td>Novartis Pharma GmbH</td>
<td>Lieferfähigkeit voraussichtlich spätestens ab erster Septemberwoche 2013</td>
<td>keine andere PZN betroffen</td>
<td>0911/273122802013</td>
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</tbody>
</table>
Onkologika-Versorgung aktuell –
(einige) Lösungsansätze

- Auflistung von essentiellen Arzneimitteln (Häm/Onk)
- rechtzeitige Information über Lieferengpass/-abbriss bzw. drohenden Versorgungsengpass durch pU

✓ Etablierung eines Registers bei BOB: BfArM/PEI
  (freiwillig?, öffentlich zugänglich, Zeitfrage …)

- gesetzliche Anpassung(en): AMG § 52b Abs. 5, § 73 Abs. 3 und § 79 Abs. 5

✓ Fortsetzung der intensiven Kommunikation zwischen (Krankenhaus-)Apothekern, ÄrztInnen, PatientenInnen ….

- Beseitigung der „Root Causes“
Economic drivers of manufacturing quality problems.

- Quality not fully transparent
- Market not rewarding quality
- Perceived low enforcement threat

Contributing factors:
- Aging facilities
- New production opportunity
- Increased price competition
- Economic downturn
- Contracting practices

Quality problems:
- Products discontinued
- Quality problems
- Delays/capacity problems