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Cancer Drug Shortages: A Critical Problem

NCI Board of Scientific Advisors Meeting

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Cancer Drug Shortages: An Undeniable Problem

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By JENNIFER CORBETT DOOREN

A shortage of a key leukemia drug that started last year has worsened, causing many major cancer centers such as the Johns Hopkins Hospital to start rationing the drug and others to turn away patients from community hospitals that have run out of the medication.

The Washington Post 04/19/2011

Without this drug, leukemia patients won't be cured

Hagop M. Kantarjian, MD

In the United States this year, about 10,000 people will receive a diagnosis of acute myeloid leukemia (AML). Since mid-December, the most effective drug to treat this fatal disease has been in dangerously short supply. The chemotherapy medication cytarabine was first approved by the Food and Drug Administration in 1969. For four decades, it has been the backbone of AML treatment. A doctor at a large center in Nebraska wrote, "We are completely out after the end of the week and no cytarabine in sight. It is like we live in a Third World country!“ "Sorry, we're out of stock" is simply not acceptable.

CHICAGO, June 7 (Reuters) - Cancer medicines desperately needed by sick children and adults are in short supply, undermining the ability of U.S. doctors to administer treatments, top oncologists warned this week. Generic chemotherapy drugs are in particularly tight supply at the nation's hospitals, including mainstay cancer treatments such as cisplatin, doxorubicin, cytarabine and leucovorin.

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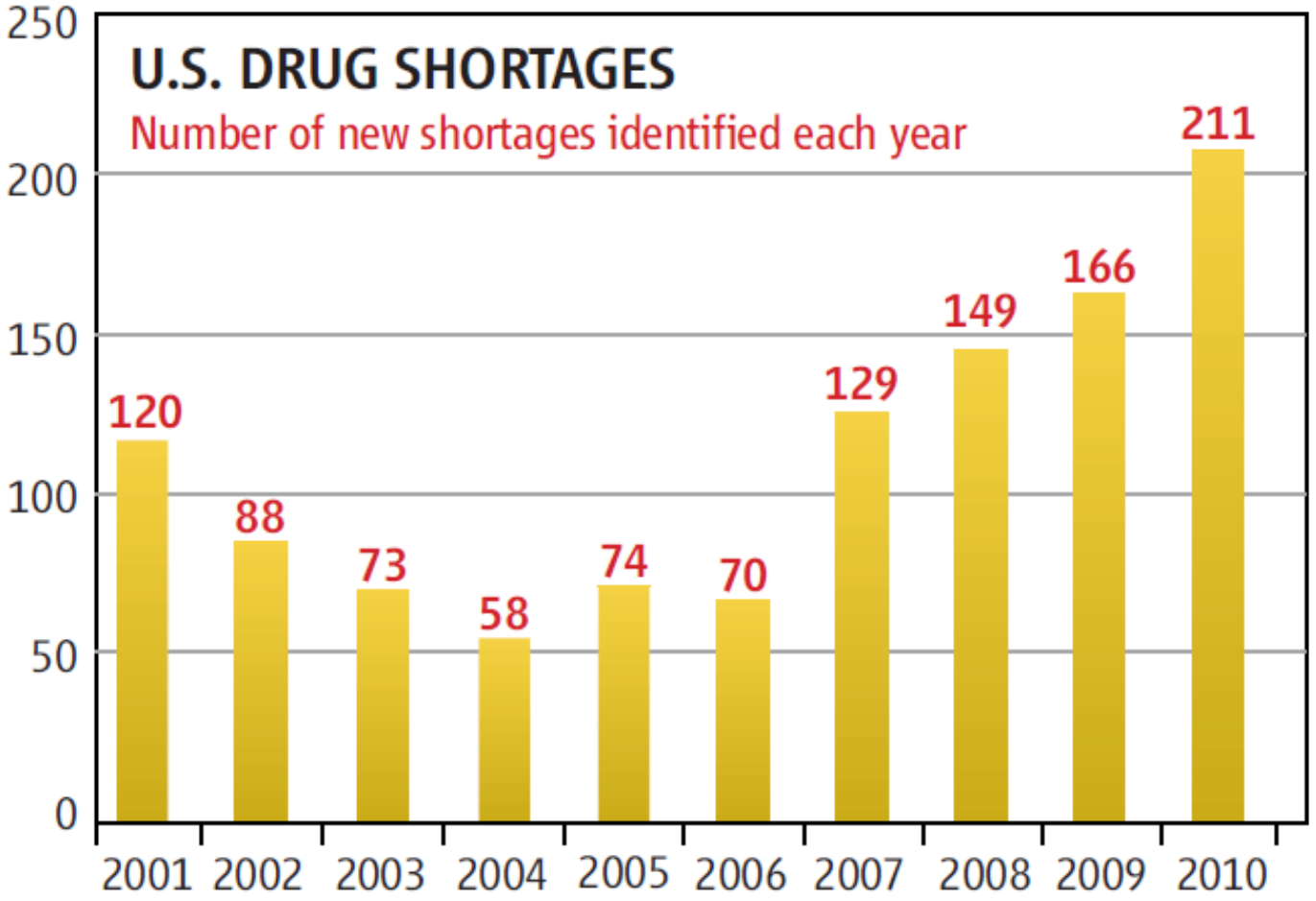
Drug Shortages: An Increasing Problem



Science 332: 523, 2011

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FDA Drug Shortage Website
June 17, 2011

200 Line Items: Not Just Oncologic Agents

67 Total Unique Compounds

10 oral
3 topical
54 injectable (80%)

10 Unique injectable antineoplastic agents

--up to 35 total 'at risk'

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FDA Drug Shortage Website (Sample Drugs) June 17, 2011

Acetylcysteine Inhalation	Doxorubicin lyophilized powder	Neupro (rotigotine transdermal)
Amikacin Injection	Erythromycin lactobionate inj	Norepinephrine Bitartrate Inj
Ammonium Chloride Inj	Etoposide solution for inj	Oxsoralen (methoxsalen) topical
Ammonium molybdate inj	Fentanyl Transdermal System	Oxsoralen-Ultra (methoxsalen) caps
Ammonul (phenylacetate/benzoate)	Foscarnet Sodium Injection	Pentosan Polysulfate sodium caps
Amphetamine Mixed Salts, ER Caps	Fosphenytoin Sodium Inj	Phenylephrine HCl Injection
Aquasol A, 50,000 units/mL	Furosemide Injection	Potassium Phosphate
Arginine 10% injection	Haloperidol Decanoate Injection	Procainamide HCL Injection
Avalide (irbesartan&HCTZ)Tabs	Intravenous Fat Emulsion	Propofol Injection
Bleomycin Injection	Leucovorin Ca Lyophilized Powder	Sodium Chloride 23.4% and 14.6%
Calcitriol 1 mcg/mL Inj	Levorphanol 2mg Tablets	Sodium Phosphate Injection
Calcium Chloride Inj	Lorazepam Injection	Succinylcholine injection
Calcium Gluconate	Magnesium Sulfate Injection	Sulfamethoxazole/trimethoprim inj
Cisplatin injection	Methylphenidate Transdermal	Tamiflu Oral Suspension 12mg/ml
Cleviprex 0.5 mg/mL	Metoclopramide injection	Thiotepa for Injection
Cytarabine Injection	Mexiletine Capsules	Thyroid (desiccated) tablets
Daunorubicin HCl inj	Mustargen (mechlorethamine) inj	Thyrolar Tablets
Desmopressin Inj	Multi-Vitamin Infusion	Tromethamine
Dexamethasone Inj	Nalbuphine Injection	Vasopressin Injection
Digoxin Injection	NeoProfen (ibuprofen lysine) Inj	Vecuronium Injection
Diltiazem Injection	Neostigmine methylsulfate inj	Vincristine Sulfate Injection

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Relative Costs: Tail Wags the Dog

$125 billion total cost of cancer treatment in 2010

$20 billion sales of non-generic anticancer drugs in 2010

$0.4 billion generic injectable sales in 2010 (N=34 drugs)

Generic Injectable Drugs Only 2% of non-Generic Sales

But 100% of Shortage Items

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Reasons for Shortages 2010

- **Consolidation in the generics industry**
  - ✓ As agent "ages" number of producers declines; no alternative drugs especially for sterile injectables
- **Raw materials availability**
  - ✓ Production of active pharmaceutical ingredients now overwhelmingly off-shore (>80% China or India); explains ~ 10% of injectable shortages
- **Supply chain**
  - ✓ Fewer suppliers with tighter inventories ("just in time" production) means less flexibility in system
  - ✓ Difficult to significantly ramp up production (if only two or three manufacturers) ~ 20%
- **Manufacturing and Regulatory**
  - ✓ Smallest number of manufacturers for sterile injectable products; complex processes
  - ✓ Same production lines for multiple products; quality recalls ~ 45% of shortages
  - ✓ Cost of filing Abbreviated NDAs and Supplemental NDAs; USP standards--changes
- **Business decisions**
  - ✓ Relatively low margins
  - ✓ Costs of changes in GMP production—factory shutdowns ~ 5%

Modified from E.R. Fox, PharmD.

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Reasons for Shortages 2010 (contd.)

- Waxman-Hatch Act of 1984 created current generic drug system
  - ✓ Highly effective at lowering drug costs via competitive market
  - ✓ Unintended consequences:
    - ➢ To lower cost of business, supply chain very tight
    - ➢ No requirement to buffer even minor disruptions
- Expectation that situation will get worse
- What can/should the FDA do?
  - ✓ If a manufacturing shortage, FDA can use regulatory discretion to mitigate risk to patients—encourage ramp up, expedite regulatory requirements for approval of increased manufacturing capacity, and in rare cases can allow temporary importation (propofol)
  - ✓ BUT, FDA cannot force manufacturer's to produce a product, and currently, cannot force a manufacturer to report plans to discontinue production unless they are a sole source
  - ✓ FDA does not make or distribute drugs—even though the public thinks they do

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Drug Shortage Summit
November 5, 2010

American Society of Anesthesiologists

ASCO® American Society of Clinical Oncology
Making a world of difference in cancer care

American Society of Health-System Pharmacists®

ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES

✓ Regulatory changes: Expand FDA authority to require manufacturer notification of withdrawals; require confidential notification of FDA when a single manufacturing source; require manufacturing redundancies as part of FDA approval process

✓ Raw materials sourcing and manufacturing: Establish communication channels to improve notification of anticipated shortages to FDA

✓ Distribution factors: Improve distribution interactions and procurement amongst group purchasing organizations

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Remedies Under Consideration

June 1, 2011 (AP) — US Senators Amy Klobuchar, (D) Minnesota, and Robert Casey, (D) Pennsylvania, have introduced the: "Preserving Access to Life-Saving Medications Act." Under the bill, drug makers would have to immediately notify the FDA when a shortage of raw materials or other problem would likely cause a shortage. The FDA would then be allowed to work with other domestic and international manufacturers to maintain an uninterrupted supply.

- Helpful in the long run; defines a new problem more expeditiously
- Does not make drugs available when there is an acute shortage
- Similarly, communication recommendations from the Summit do not alleviate current, severe shortages

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Generic Drug Shortage Hinders NCI Clinical Research Programs

- **NCI sponsors clinical research studies that include these generic drugs as part of comparator groups and as add-ons with investigational drugs**

- **Investigators in these research studies report:**

  - ✓ **Inability to enroll new patients when drug supply not assured**
  - ✓ **Patients on-study receiving alternate drugs when supply not available**
  - ✓ **Concern about interpretation of results when drug substitutions occur**

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Is There a Role for the NCI to Work with FDA to Alleviate Cancer Drug Shortages?

- NCI has more than 50 years of experience in making and distributing drugs

- The NCI infrastructure for new drug development could be leveraged to provide short-term supplies for individual drugs as shortages emerge

- NCI staff can work with together with FDA-HHS and professional societies to formulate **long-term solutions** in the **private sector** – for **all** therapeutic categories

- NCI action could stimulate leadership in other diseases

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Short-term Options to Consider

- NCI could acquire and distribute finished drug products
  - ✓ Primary difficulty—vials not available for purchase during shortage; does not expand total available supply; could exacerbate acute shortage
  - ✓ Expiration dates of finished products mandates continuous updating
  - ✓ State-by-state licensing for distribution of finished drug products
  - ✓ Most expensive option and requires longer time to build reserve
- NCI could acquire and distribute bulk drug supplies
  - ✓ The active pharmaceutical ingredients (API) could be acquired for storage by NCI, and distributed during period of shortage
  - ✓ In general, most active ingredients are not in short supply even when the finished drug supply is in a severe shortage
  - ✓ Cancer Centers, hospitals, and other organizations can prepare and dispense final drug solutions for patients as established in the USP compounding monographs
  - ✓ Requires considerable advance planning re: supply chain, risks of using compounded drug
- FDA might take role of defining beginning/end of shortage and assisting NCI in selecting drugs to be acquired

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Potential Consequences

Positive	Negative
• Alleviate short-term (~ 3-4 month) shortages of injectable generic anticancer agents; immediate clinical benefit	• Long-term dependence on NCI reserves might delay legislative action
• Guarantee availability of iv generics used in NCI-supported clinical trials	• Cost of drugs, drug storage, drug distribution, and mechanisms for setting up appropriate system for allocation
• Provide time for regulatory and/or legislative actions to facilitate market-based solutions	• Potential risks of using compounded rather than vialed agents
• Enhance NCI/NIH interactions with FDA	• If use API, availability limited to sites with compounding pharmacies

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“No Sign of Abating”

Dr. Richard Schilsky, cancer specialist at the University of Chicago and a past ASCO president, said the shortages have been going on for about nine months with no sign of abating. "When you talk to the drug companies, they say there are manufacturing problems or they are taking plants offline then it takes a while to get them back up," he said. "They point the finger at the FDA, saying the FDA is under-resourced and they can't get plants inspected to allow resumption of drug production. “The drug suppliers are in the middle of this as well," he said.