Chemotherapy Drug Shortages in the United States Revisited

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The shortage of cytarabine, a drug critical for the cure of acute myeloid leukemia, entered public consciousness in early 2011. This resulted in the mainstream media publicizing the problem of chemotherapy shortages in cancer. Analyses identified several reasons for the drug shortages: shortages in supply of raw materials, production problems, contamination of materials, aging production plants, limited inventories of generic drugs (to reduce company costs), limited profit margins, possible US Food and Drug Administration (FDA) overregulation and long timelines to approve new sources of generics, and others.[1-4] The practices of the group purchasing organizations (GPOs) have also been recently highlighted by several sources as a potential major root cause of generic chemotherapy drug shortages.[5-9]

Drug shortages are almost uniquely associated with generic drugs (small profit margins) and rarely with patented drugs (large profit margins). Also, they are more common in the United States than in Europe and elsewhere, where generic drug prices are on average higher. This suggests the main cause of drug shortages to be economic: small profit margins that discourage generic companies from competing for a share of the US generic chemotherapy market.

The analyses also uncovered drug black marketing strategies. In essence, some intermediary distributors, including well-meaning large hospital conglomerates and pharmacies, that become aware of drug production problems with an aging plant or with supply of raw material, stockpile particular drugs in large quantities in order to protect themselves from shortages. This, in part, precipitates the drug shortage, which then allows unregulated vendors to sell the drug at huge markups, sometimes 600% to 8,000% of the original prices.[10] Drug shortages are not only harming patients, but they may be costing our health care system from $200 to $300 million annually as a result of the drug black market and the increased infrastructures required to manage the shortages.[10,11]

As a result of these concerns, President Obama issued an executive order in October 2011 that instructed the FDA to require manufacturers to give advanced warning of potential shortages (at least 6 months) to allow the FDA to prepare for and avoid drug shortages.[12] The Gray Market Drug Reform and Transparency Act of 2013, sponsored by US Representative Elijah Cummings, proposed to ban the practice of "gray market" drug sales.[13]

Three years later, chemotherapy drug shortages continue to threaten patients' lives.[7,14] Although the substitution of some chemotherapy drugs in short supply with others may be possible, many, like cytarabine, cannot be substituted. Moreover, including substituted agents in established curative regimens may lessen the chances of cure, modify the toxicity profiles, or lead to uncertain results.[15]

The Government Accountability Office (GAO) issued a report in February 2014 confirming the persistence of drug shortages, mostly generic, as a threat to public health care.[4] In 2012, there were 261 ongoing drug shortages, and 195 new shortages. The numbers in 2013 may be better. A *New York Times* article reported that "what drives shortages is often a mystery. The drug industry rarely spells out the precise reason for shortages, citing its need to protect competitive trade information."[14] However, the mystery is obvious: economic forces.

There are at least four potentially modifiable reasons behind chemotherapy drug shortages: (1) the Medicare average sales price (ASP) + 6% rule (resulting in low generic drug prices and few competing generic companies), (2) the drug black market, (3) the FDA oversight mechanisms, and (4) the GPO practices.

Before 2003, Medicare reimbursed 95% of the average wholesale price of a drug. Because of the unregulated manufacturers' prices, oncologists bought drugs at lower prices (66% to 88% of the ASP), and sold them at higher prices in their offices, making good profits (20% to 50%). This good profit margin encouraged doctors to practice in more rural areas (less competition, more profits), and made it easier for patients to receive care in nearby offices. This practice also lowered costs, as it is cheaper to give chemotherapy in doctors' offices than in hospital settings.[16,17] The Medicare Modernization Act of 2003 introduced a well-intended legislation to prevent excessive profits, referred to as "Medicare ASP + 6%." The new Medicare formula for reimbursement of physician-administered drugs under Part B was capped at 6% the ASP, in essence at 6% profit on the drug sale price. This actually barely covers pharmacy costs for receiving, inspecting, storing, and dispensing generic drugs. This also made it difficult for manufacturers to raise the drug prices more than 6% in any 6-month period, and left little flexibility for prices to adapt to free-market supply and demand. The Medicare Modernization Act was implemented in 2005. Chemotherapy drug shortages escalated in 2006 and have increased drastically since 2008. In Europe (no Medicare + ASP 6%–like rule), generic chemotherapy drugs prices are on average higher and, because of better profit margins, multiple generic companies remain in the market. Consequently, there are fewer chemotherapy drug shortages.

Changing the ASP + 6% rule to allow more profits may worsen the situation with the already very high prices of patented (brand) drugs, which have recently routinely increased by

10% to 12% annually. For example, the price of imatinib increased from $28,000/year in 2001 to $92,000/year in 2012.[18,19] However, establishing a bottom price for generics (perhaps 3% to 5% of patented drug price), or changing the Medicare reimbursement formula to ASP + 10% to 20% only for generics, could help improve market forces.

The GAO report credited the FDA for preventing some potential drug shortages but was critical of shortcomings in managing the drug shortage data that could ultimately hinder the FDA's efforts to prevent shortages.[4] A report by the House of Representatives Committee on Oversight and Government Reform, chaired by Representative Darrell Issa, was more blunt in blaming the actions and regulatory activities undertaken by the FDA since 2010 (when Dr Margaret Hamburg was appointed) as the primary reason for the severity of drug shortages. But this report may have had some political undertones.[7]

Several sources and organizations, for example, Physicians Against Drug Shortages (PADS), have recently highlighted the engagement of GPOs in practices that may be causing generic chemotherapy drug shortages.[5-9] GPOs were originally formed in 1910 to leverage their collective purchasing power to keep costs low for their customers. They collected their fees from hospitals to secure the best possible prices for medical supplies, including prescription drugs. In 1987, a "safe harbor" provision added to the Social Security Act an anti-kickback statute that allowed shifting the fees paid to GPOs from the buyers (hospitals) to the sellers. Under the GPO safe harbor provision, these administrative fees theoretically have a soft cap at 3% of sales. Fees above the 3% limit require the GPO to disclose the percentage of the administrative fees to the Secretary of Health and Human Services (HHS). GPOs control the purchasing of $300 billion in drugs, devices, and supplies for about 5,000 hospitals. These analyses[5,6,9] argue that GPOs have strayed from their original purpose and are engaging in practices that increase their profits at the expense of suppliers (generic drug manufacturers). In the GPO system, vendors may be competing for exclusive contracts based on "pay-to-play," that is, who pays the largest fees to be included, not who supplies the best products at the best price. DeRoo suggested that some of the fees paid to GPOs frequently amount to 20% or more of the total sales prices, but they may be hidden under other nonadministrative fees labels to avoid the annual reporting to HHS.[5] This, together with the small profit margins, effectively marginalizes smaller manufacturers and reduces the number of competing generic companies.

Today, as a result of market consolidations, six major GPOs account for more than 90% of the total contracts volume,[5] and only six generic companies compete for the generic chemotherapy market in the United States. Therefore, GPOs and the upstream suppliers appear to be operating more recently as oligopolies, which might raise concern about anticompetitive behaviors.[5]

Zweig and Campbell contended that the GPOs exclusionary contracts and "outrageous and undisclosed fees" have reduced the number of competing generic companies to few (one or two for each drug), and are the root cause of many generic chemotherapy drug shortages.[6,9] These concerns are certainly worth investigating, in particular, (1) the actual average administrative fees paid by the manufacturers to GPOs, (2) whether they result in exclusionary strategies, and (3) whether they inflate costs (by approximately $30 billion as reported in one article).[9]

Solutions to alleviate the generic chemotherapy drug shortages may include (1) establishing bottom prices for chemotherapy generics, and/or keeping ASP + 6% for brand drugs, but changing the formula to ASP + 10% to 20% for generics; (2) requiring the FDA to establish clearer warning signals for potential drug shortages, strengthening its drug shortage data, conducting periodic analyses on shortages, reacting more promptly to importation of similar generics before shortages occur, and encouraging strategies that bring more generic companies into the US market[3,4]; (3) enforcing the illegality of drug black market strategies; and (4) critically reviewing GPO practices, in particular, potential anticompetitive approaches that result from high fees paid by manufacturers in order to enter the GPO-controlled markets.

Author's Disclosures of Potential Conflicts of Interest
The author indicated no potential conflicts of interest.

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DOI: 10.1200/JOP.2014.001514

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