



The Shortage of Essential Cancer Drugs and Generics in the United States of America. Global Brain Storming Directions for the World.

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Summary

The shortage of the older essential cancer drugs that are off patent, mostly generics and injectable, has its threatening impact on health of cancer patients, clinical trials and the burden of costs spending on the health system in the United States. The problem is multifactorial and mostly economical and due to lack of incentives for production. Complex problems have no single or simple solutions. In order to get several effective proposals and solutions, then, there should be openness for thoughts and ideas. The solutions could be short term and long term. Also, it could be regulatory market, legislative or non market measures.

Conclusion: We consider that there is a lot that could be thought for the US and the world if we tackle the issue globally in the context of the availability and affordability of economically sustainable better value cancer drugs regardless they are brand or generic and aiming at win-win outcome for all stakeholders. This could be a model for application of "The Fourth Way" that was proposed as a new pragmatic approach for problems with economic drivers in the USA and the World and not only for the problem of shortage of a number of cancer drugs.

Keywords

Cancer drugs, Cancer treatment access, Cancer chemotherapy, Global health, Health economics

Background

Drug shortage is a complicated issue that effects relatively older and off-patent drugs as well non-generic drugs, in the USA. In 2011, there was shortage of almost 300 drugs including antibiotics, anesthetic agents, antihypertensive medications, common electrolyte solutions and around 22 cancer drugs. The impact of shortage is harder on oncology than other specialties. There is growing concern

over the shortage of other supportive care drugs, such as antiemetics and pain medications, and basic IV fluids and electrolytes [1,2]. In a previous article, we made a comprehensive review on the variability of the availability of cancer generics drugs in the USA [3]. The list of drugs includes: bleomycin, busulfan, carboplatin, cisplatin, chlorambucil, cytarabine, doxorubicin, fludarabine, etoposide, leucovorin, mechlorethamine, methotrexate, nitrogen mustard, paclitaxel, thiopeta vincristine, and morphine [1]. The alternatives to these essential cancer drugs are expensive, increase financial burden, and are not as efficacious.

The availability of cancer drugs improved slightly in April 2013 because the FDA, pharmacists, and physicians worked in conjunction with drugs manufacturers to resolve the scarcity issue. However, this temporary solution is insufficient as it only allows for the practice of medicine from crisis to crisis and many other drugs remain in shortage. The underlying economic issues and lack of incentives for production need to be addressed to arrive at innovative and permanent solutions for this continuing predicament [4,5]. The purpose of this article is to present ideas and proposals for solutions with special emphasis on exploring scientific avenues that take into consideration the interests of different stakeholders and the notion of economically sustainable and affordable cancer drug therapy and cancer care in the world [6,7].

Short-Term Solutions

In order to understand this issue it is imperative to delve into the short-term measures that are currently in practice. The FDA has taken steps to alleviate some of the most critical oncology drug shortages [4]. Through August 2012 there were 123 new drugs in short supply, about 33% less than a year earlier. In the second quarter of this year 2012, there were 211 active shortages, down from 246 reports in the

second quarter of 2011 [8]. FDA officials attribute the improvement to efforts the agency made after President Obama issued an executive order in October, 2011. Accordingly, The FDA gets early reports from companies about potential shortages [9]. One short term solution is to set priorities in determining shortage. Some centers now have a red-yellow-green system for quickly recognizing developing shortages in supply and determining which patients get priority [10]. Among the recent practical approaches, at Duke University Medical Center, USA, describes their policy to manage shortages of medications. When bleomycin sulfate became not enough, all eligible patients were informed to come to the clinic for administration of bleomycin on the same day to limit wastage from single-use vials. Doses were rounded to the nearest number to minimize wastage. The hard decision was to delay treatment for patients if the hospital could not ensure a complete course of treatment and to only accept referrals from their nearby region. This policy has been described as an ethical approach for allocating inadequate resources in hospitals [11]. Hospitals have also purchased drugs in the gray market to compensate for the inadequacy [1]. However, this option introduces safety and quality-control issues in addition of purchasing drugs at higher prices.

Another short-term solution was to import generics from other countries. In February 2012, The US Food and Drug Administration (FDA) approved, importing some unapproved drugs that could serve as temporary alternatives. Lipodox, a substitute drug for doxorubicin, was imported from India, for use by the biopharmaceutical company Endocyte in a clinical trial comparing its investigational drug EC145 with doxorubicin. In addition, FDA announced the approval of a new manufacturer of a preservative-free formulation of methotrexate [4,12]. It is likely that the FDA will contact drug companies in other countries to assure that drugs of good quality will be imported, however that can create shortages in those countries [12]. While drugs shortages ease remain a serious problem, this will continue unless more sustainable solutions are proposed [7].

Economic Incentives, Market and Pricing Solutions

Europe has not been as severely impacted as yet due to its policy of pricing of generics in West Europe. Prices are set higher for generics so that companies are motivated to manufacture them. Further the prices of brand-name drugs are often much lower than US prices [10]. However, Europe will endure drug shortages due to other issues. Britain faces worsening shortages of medicines because vital supplies are being sucked out of the country by exporters who can sell them for higher prices elsewhere. The All-Party Pharmacy Group (APPG) in UK said that the government needed to consider ways to limit this so-called parallel trade, allowed under European Union rules and which can distort the distribution of prescription drugs. Action by drug manufacturers to introduce quotas for drugs in a bid to stop exports has made the situation worse. In Greece where the government has cut prices for certain medicines by a quarter, leading to increased exports and parallel trade [13].

Market Solution takes one of two approaches, either laissez-faire, thereby accepting uncertainties (that would be corrected by the market) or tight regulation, thereby setting a floor for the average sales prices (ASP) of generic drugs. However, this would increase the total cost of cancer drugs unless the price of branded products is reduced at the same time as in the case in Europe. The objective is to create more incentives to manufacturers of generics [10]. The price of 1g of cytarabine ranges from \$12 to \$16. The average price of a vial of carboplatin is less than \$5. Under the Medicare reimbursement system, limitations on price increases may mean certain generic drugs will never be profitable enough from a manufacturing standpoint. One alternative would be to set a minimum price for generics based on some comparison with a similar brand drug. For example, if a brand drug costs \$50,000 per year, the generic drug may be priced at 5% to 10%, or \$2,000 to \$5,000 per year [5]. This same point is emphasized by Dr. Chabner who stated that the US could still afford higher prices for drugs [14,15]. But generics account for less than 2% of the cost of cancer drugs, hence, raising the price of generics, would have minimal effect on the cost of cancer care.

The Possibility of Increasing Incentives for Production of Generics

There is an extensive untapped capacity to produce generics in Europe and Asia. Major pharmaceutical companies, such as Pfizer and Sanofi, have generic products, many of which are sold exclusively overseas. In recent months, Pfizer has commenced marketing two drugs, irinotecan and doxorubicin, in the United States. These drugs were formerly produced on patent in this country. Sanofi has offered to make its extensive list of common generics available in the United States. Major pharmaceutical companies could re-enter the market for off-patent products, but they need the incentives of a reasonable profit and an expedited route to marketing approval [15].

Even as Big Pharma observes a critical patent issue in India to see how restrictive the country intends to be, there was an indication that the country welcomed outside investments in the domestic industry. In 2010, Abbott Laboratories bought Mumbai-based Piramal Healthcare's Indian business for \$3.72 billion. And Japan's Daiichi Sankyo laid out \$4.2 billion in 2008 to get controlling interest of India's giant generics maker Ranbaxy Laboratories. However, public opinion turned against international pharma as the concern grew that they would inflate drug prices in a country where much of the population is still in deep poverty. The drug manufacturers cannot stop manufacturing any cheap drug they currently produce and they will have to keep investing with Indian partners for 5 years. There is a discussion in India about enforcing new price caps on branded drugs, hence this add another new concern for branded drug manufacturers [16].

One of the directions that should be studied deeply, albeit, with much prudence is to drop patency of brand drugs to be manufactured in less affluent countries. On April 1, 2013, the Indian Supreme Court handed down a judgment on a patent for Novartis for the application for imatinib mesylate (a beta crystalline form of imatinib) under section 3(d) of the Indian Patents Act, which prevents a patent being taken out on a new version of a known molecule that does not make the compound significantly more effective. Despite the exciting titles and texts that appeared in *The Lancet Oncology* "Is India ready to lead the battle for fair access to medicines?" [17] and in *The Lancet* "India's patent case victory rattles Big Pharma" [18] It may not lead to a global fair access for cancer drugs in India and the world. Although it is imperative that cancer patients in India and the world have access to affordable cancer care and therapy, India's decision raise immediate concerns about the intellectual property rights and investment in innovation of treatment. Further, it could have a contrary effect on the access of newer drugs as companies may be motivated to increase benefits from sales at the initial stages but do not have incentives for production of these drugs in the following years as the patency period approaches its conclusion, thereby complicating the problem. Moreover it could have negative effects on investment provisions in the proposed free-trade agreement between India and the European Union, and other potential agreements.

Repurposing Drugs to Improve Profits and Incentives for Production

Scientific exploration of existing cancer and non-cancer drugs utilized as single or as new combinations could lead to potentially viable therapeutics [6,7]. There are examples like the metronomic use of prolonged, low oral doses of the inexpensive drugs, cyclophosphamide and methotrexate, as palliative breast cancer treatment [19]. In a phase II trial of postmenopausal women with advanced, aromatase inhibitor-resistant, hormone receptor-positive breast cancer, the low dose (6mg/d) oral estradiol was as effective (around 30%) as the conventional high dose (30mg/d) and presented with less adverse events [20]. A preliminary investigation of the repurpose of the currently available drugs ritonavir, used for HIV treatment, and the metformin, used for diabetes revealed that there is a remarkable synergy that shows promise in multiple myeloma [21].

Researchers have performed the 300,000 experiments to test 5,000 different combinations of 100 approved cancer drugs in each

of 60 cell lines developed by the National Cancer Institute (NCI). The cell line panel, known as the NCI-60, is commonly used by cancer researchers worldwide. The new repository of data will eventually be made available to the public on the NCI Development Therapeutics Program's website [22] with the intent that it will provide investigators insight into potential drug combinations to target or avoid. By providing the new insights, the NCI hopes to accelerate the advancement of novel therapeutic combinations that demonstrate minimum side effects and maximum promise. The confirmation of these results will form a basis for future clinical trials of such combinations [23].

Repair the System of Compensation of Oncologists

To create a sustainable system it is imperative to examine the issue from the oncologists' perspective as well. The oncology is a cognitive specialty without many associated procedures that allow for financial enhancements. Hence, many private oncologists in the USA depend on the incentives of the drugs prescription reimbursement. The system must be repaired so that oncologists may be properly compensated for their services, thereby limiting any ethical conflicts. Further, patients should have access to information regarding revenues that might influence oncologist's drug choices and thus affects costs and copayments [10].

The first proposal is to pay physicians salaries, as most academic centers do, so that oncologists do not have to rely on chemotherapy sales for income. Hence, there is a proposal to raise the reimbursement add-on to the price of a drug price from 6% to 30% [15]. The second proposal is to adopt clinical pathways for which practices are paid disease management fees that are not based on chemotherapy sales [6,10,15]. The New York Times recently published a plan to overhaul cancer care in the US that suggests the payment system needs to move away from fee-for-service and towards a system of bundled payments. This is not far from the European idea of "Remuneration for the act of Oncologists" which involves payment of one fee for all the services rendered in caring for a cancer patient. Hence, the oncologist would be paid for a consultation or advice or part of the diagnosis or the treatment he did regardless he/she prescribed or not and what he/she prescribed [24]. This would remove the incentive to prescribe more expensive drugs when older generics are equally effective [25,26]. The third proposal involves "Remuneration for Pharmacists" depending on the number of prescription served regardless of the content and number of drugs present in the prescriptions. It may be an audacious idea, however, innovative solutions need to be generated particularly when faced with a complicated problem.

The Prescription Drug User Fee Act (PDUFA)

The compromise bill closely mirrors the bills passed by the House and the Senate in May, 2012. The newest version of PDUFA would augment industry user fees by 6% in exchange for improved communication with the agency as well as greater steadiness in the drug approval process. That increase would result in pharmaceutical companies paying \$713 million in user fees for fiscal 2013 and a higher amount in the remaining 4 years.

The user-fee agreement would also reauthorize the Medical Device User Fee Act (MDUFA), under which device companies pay the FDA user fees that cover about 20% of FDA's device review expenses. The MDUFA agreement would allow the FDA to more than double the user fees it collects from device manufacturers, giving it \$595 million in user fees from 2013 to 2017. That money would go toward speeding the approval of new devices, which has been a major source of argument in recent years among the agency and device companies who think the process is too slow and convoluted. The bill also would allow for an independent entity to evaluate the process the FDA uses to approve new devices, and the FDA would have to implement a plan to address any deficiencies identified by the independent board. The compromise bill also would give the FDA the authority to stop a clinical trial of a device if the agency determines that the device causes an unreasonable safety risk. Moreover, the bill also creates new user-fee programs for two industries that do not

currently have such agreements: the generic drug industry and the generic biologics industry.

The user-fee agreement with manufacturers of generic biologics or biosimilars, known as the Biosimilar User Fee Act, would at first be funded with \$20 million annually from the federal government to hire new FDA staff and assist in creation a procedure to review and approve generic versions of biologic and biosimilar product development (10% of the PDUFA fee). The bill also encompasses drug by requiring the secretary of Health and Human Services to make available a list of all current shortages [27].

The deal with the generic industry would allow the FDA to collect about \$299 million a year from generic drugs manufacturers for 5 years. Generic drug trade groups have called on the FDA to step up its inspections of foreign drug factories. The user fees will largely go toward increased inspection of foreign factories, which is where 80% of all ingredients in drugs sold in the U.S. are manufactured. There is reportedly an accumulation of more than 2,000 unapproved generic applications, with a median time to approval of 30 months. The generic drug user-fee deal will also lead to the employment of more inspectors, which could cut down on the time needed to approve a new generic drug. It is imperative that the FDA allocate the resources needed to significantly decrease this timeline to approval, thus allowing more competitors into the generic market within the 6-month timeline of the anticipated drug shortage. The production of adequate capacity would significantly reduce the presence of gray-market players [5,28].

Coalitions of Oncologists

Another small but potentially significant step to address drug shortages and related problems is the formation of a not-for-profit coalition by a group of eminent oncologists in the USA. The newly formed Citizens Oncology Foundation (COF) intends to address the short supply of cancer drugs via utilization of a variety of strategies. One goal is to import drugs from the same sources that supply Western Europe. Another is to develop drugs that would be as effective but far less expensive than currently available drugs. For example, endoxifen, the metabolite of tamoxifen, is just as effective as tamoxifen and much cheaper to make. However, endoxifen is not marketed in the United States because it is cannot be protected by patent and thus cannot guarantee a profit, but this is less of a factor for the not-for-profit coalition. The primary objective is to become an alternate pathway for drug discovery, development and researches [29].

Profits after the Period of Patency

These original drugs have already been tested for clinical efficacy and have a proven track record due to the utilization by patients. Therefore, strategies should be developed to maintain the accessibility and the affordability of these cancer drugs following the end of patency. Prices of original drugs should be renegotiated and considered for a price decrease by the manufacturers. Further, these drugs should be given priority for purchase by the authorities even if there is a pre-defined percentage of difference in prices with competing with new generics. Newly developed drugs should have a defined price during the patency period. Following this period, the price of the drugs would undergo an incremental decrease so that manufacturers may continue to gain a marginal profit from production. Patients will be treated with drugs of known clinical efficacy and this could be important for the validity of multi-centric clinical trials if variable names of generics are used when the use of the essential cancer drugs are part of the protocol of testing newer drugs. The continuation of gaining some profits following patency period could encourage the scientific exploration and innovation by brand drug producers. Therefore, ensuring a system that is lucrative for the parties involved.

Suggestions Regarding the Issue of the Importation of Generics

When purchasing US produced generics in the US, priorities should be given to purchases of active ingredients of the drug from

the originals companies. However, if the generics are being imported from developing countries, then priorities for importation should be given to joint venture manufacturers that have arrived at a bilateral agreement of surveillance and transfer of the knowhow with the original companies. This will ensure the quality of products and would also give opportunities to industries and workers in these countries. There by, increasing the potential of investment and progress of production of drug generics of good quality in less affluent countries.

Pricing of Drugs in Affluent Countries

It is an issue full of complexities as well as variability in different countries. However, it is worthwhile to evaluate the suggestion to have balanced prices that assure availability of the essential and new drugs to members of the Organization for Economic Cooperation and Development (OECD). The OECD comprises of the countries of North America including The USA and Canada, some countries in Europe and South America as well as Japan, Australia and New Zealand. This may help manufacturers of these drugs to propose a decrease of prices for middle income countries, and another more decrease of prices in low income countries. Hence, this may result in increasing the competition to provide affordable cancer drugs of good quality in less affluent countries, with international measures against smuggling of low price drugs. Thinking globally could bear clues to complicated problems in rich countries and to other problems in less affluent countries. This would reveal that there are possible positive aspects of globalization. As David Kerr stated, "For me, globalization is about convergence, If we look at cancer patients, whether in Beijing, New York, Hamburg, or wherever, of needs and requirements of us, so there is something about convergence of quality, of us driving our science and medicine forward, of meeting the needs of our patients"[30].

Governmental Purchase of Drugs Patents and Public Funding of Clinical Trials

Dean Baker, the co-director of the Center for Economic and Policy Research CEPR in the US, suggests that the system of patency, created in the 15th century is inconvenient for the 21st century. He supports the ideas of Joseph Stiglitz, the winner of Nobel Memorial Prize in Economic Sciences in 2001, Chairman of Economic Advisers of Former President Bill Clinton, and former Vice President of the World Bank, and others who suggested that governments would buy the ownership of patency of drugs, thereby assuring the production of affordable cancer drugs for long years. Further, the suggestion is to increase the research budget, hence, the outcome and financial gain of innovation and discoveries would come to governments. One of the examples is the National Institutes of Health (NIH), USA [31,32]. According to the studies of Dean Baker, the publicly funding drug trials would result to more benefits to governments [31]. It is worthwhile to note that they are not encouraging the self-correcting nature of Laissez-Faire, nor are they supporting the current regulations. These opinions came from highly distinguished economists and should be taken into consideration while studying solutions for the complexities of availability of cancer drugs.

Future Directions

Among multiple factors, the main obvious cause for the shortage of cancer drugs generics is economic and particularly the lack of incentives for production. More scientific explorations and studies are aimed towards the economical sustainability and affordability of drugs rather than its brand name or generic nature. Searching for solutions for a problem with complexities like the shortage of cancer drugs generics allows for the scrutiny of the underlying issues that affect the US and the world. There by, potentially producing a model for the resolution of other issues those are impacted by economic elements.

The last two centuries have only developed three choices that guide the policy and economic issues of a country in a predetermined way. It could be fixed around either a) Laissez-faire i.e. unlimited liberalism and historical capitalism, b) Tight regulations and

legislations i.e. like the historical Marxism, or c) a Mixed Economy. However, there is a "The Fourth Way" [3,33] which proposes that the notions of liberals markets and economy of the older systems can be revised. This system would function such that the next generation would see a flexible system that continuously evolves and leads to improvements that impact all stakeholders. Application of such a system in the field of oncology would create economic sustainable and accessible cancer care as well as promote innovation in drug manufacturing [6,7].

In summary, this proposal of "The Fourth Way" [3,33] encompasses the following: 1) Identifying of goals, aims and objectives, 2) Creating strategies that reflect flexible tactics that are not ingrained with predetermined theory, 3) Utilizing the information garnered to generate innovative ideas that could realize goals, 4) Ensuring legality and ethical scientific standards, 5) Considering the humanitarian aspects and quality of life 6) Maintaining economic sustainability and scientific progress [3,6,7]. This proposed concept of "The Fourth Way" could give insight to develop a novel framework in economy and politics which could be utilized prudently for the welfare of all stakeholders.

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