High Price of Prescription Drugs & the Lack of Generic Competitions

Many factors can be considered for why prescription drugs cost so much and are rising so fast? To name a few are the drug shortages, supply disruptions, or consolidation in the Generic drug industry? However, none of them are as critical as the lack of competitions to the Brands.

With a shortage of competitors, price spikes have become the new normal. For many prescription medicines, there are only one or two companies in the U.S. responsible for the entire country's supply. Not only do these market duopolies, or more often monopolies, put us at an ever-increasing risk for drug shortages, they also create unhealthy markets, giving manufacturers pricing power – with little competitive friction that historically has kept pricing in check. In 2015, Martin Shkreli, recognized that no other generic companies were manufacturing **Daraprim**, a drug used to treat infections common among people with AIDS, increased the price from $13.50 a pill to $750, confident that no generic competitor was around to cut into his market.

The price of generic **Digoxin** (a heart medicine) and **Doxycycline** (an antibiotic) increased ten-fold. The cost of **Lantus**, brand-name insulin that's a mainstay of treatment as a long-acting drug that helps people with diabetes stay under reasonable control, saw a 54 percent price increase in 2014 alone even though it's been on the market for decades. The maker of Insulin Sanofi has filed a suit against Merck and Mylan to avoid the production of generic (biosimilar) version of Lantus its blockbuster Insulin.

When generics provide Americans with nine out of 10 of their prescriptions at only 23 percent of total spending on drugs, it is hard to fathom why anyone would call this system broken or insist that the Government should take control and command the business of developing, manufacturing and distributing these medicines.

Earlier this year, **Senator Elizabeth Warren** and Representative Jan Schakowsky disclosed the "Affordable Drug Manufacturing act."

This bill would establish an Office of Drug Manufacturing that would be required to manufacture at least 15 different generic drugs in its first year, where the agency determines there is a failure in the market. The senator insists that this is not to replace the market but to fix them and the Government trying to repair the system, not to take over. However, in our view, it would take a lot longer to build a factory and get it FDA-approved, and There's also not a one-size-fits-all drug manufacturing plant, so different products would require various machinery. Currently, there are numerous FDA approved pharmaceutical manufacturing facilities with diverse expertise in the U.S. that have no Generic customers.

Senator Warren is one of several senators who have introduced bills targeting the pharmaceutical industry. To name a few, **Sens. Jeff Merkley** (D-Ore.), **Kamala Harris** (D-Calif.) and

Amy **Klobuchar** (D.-Minn.) introduced the **CURE High Drug Prices Act**, which would allow the Federal Government to block price increases on certain drugs. **Senator Merkley** put forward separate legislation, the Low **Drug Prices Act**, weeks earlier. And **Sen. Bernie Sanders** (I-Vt.) introduced his bill, **the Prescription Drug Price Relief Act**, in the last year. **Senator Durbin** (D-Ill) also introduced a new proposal. The ***FLAT Prices Act.*** The bill would reduce the FDA-granted exclusivity period for a drug whose price increases more than 10 percent in a year, or similar amounts over a multi-year period. Drug manufacturers would be required to self-report their price spikes to the Department of Health and Human Services (HHS), and they would have the opportunity to provide an appeal to justify such a price increase. Failure to report such a price hike would incur additional reductions in market exclusivity. Under the ***FLAT Prices Act,*** the company's unjustified price spikes would trigger a decline in its monopoly period, resulting in new competition from lower-cost generic drugs sooner.

But none of these bills invites entrepreneurs and small businesses to get involved! Even though both the mechanism of participation and the government agencies to accelerate the process are all already exist and need to be defined in broader terms to allow the generic drug developers to participate.

The Government Program:
The **SBIR program** was established under the **Small Business Innovation Development Act of 1982**, (SBID Act of 1982) to attract and assist Innovative small businesses to participate in Federally-funded Research & development. Through a competitive awards-based program, **SBIR** (Small Business Innovative Research) program enables small businesses to explore their technological potential and provides the incentive to profit from its commercialization. The program's purpose is to stimulate high-tech innovation, American entrepreneurship, expand Government specific R&D needs, and, most importantly, build a robust national economy.

Mechanism of Participation
The mechanism to provide funding for some of the best early-stage innovation ideas, those ideas that, however promising, are still too high risk for private investors, including venture capital firms, has been well-defined. The SBIR program agencies award monetary contracts or grants in phases 1 & 2 of a three-phase program.

- Phase 1, the startup phase, makes awards of "up to $150,000 for approximately six months of support [for] exploration of the technical merit or feasibility of an idea or technology."
- Phase 2 awards grants of "up to $1 million, for as many as two years," to facilitate the expansion of Phase 1 results to commercialization. Up to 2014, Phase II grants were awarded exclusively to Phase 1 award winners, but in 2014 the DOD, NIH, and other agencies were allowed to make "direct to Phase 2" awards.
- Phase 3 is intended to be the time when innovation moves from manufacturing into the marketplace.

The program has been extremely successful and created companies such as **Symantec, Qualcomm, Da Vinci Surgical System, Jawbone, Lift Labs, Natel Energy, and iRobot**, which received early-stage funding from this program.

Currently, the SBIR program does not support Generic drug development. The reason given by the agency is:

"SBIR grants have a heavy emphasis on innovation, and generics don't tend to do well in peer review. Having said that, everybody is welcome to apply, but they will need to convince the reviewers of the significance, innovation, and competitive advantage. And that's a high bar for the development of generic drugs".

In other words, since the innovation is in the drug discovery and Generics Developers are copying the known knowledge and not inventing the new idea; therefore they are not in the spirit of the Small Business Innovation Development Act of 1982 (P. L. 97-219).

The logic of the SBIR program for the "Commercializing a New Drug" is that if an innovative idea has a merit "to be commercially successful," it is qualified to be funded for demonstrating the feasibility and the delivery of a "proof of concept." If successful, then in phase 2, the project is qualified for further Federal funding for the scale-up and manufacturing. Marketing and distribution of the commercial product are expected to be funded by capital ventures, banks, and big pharma (*phase 3*).
Interestingly and equally in the same order, commercializing a "new Generic drug" requires following the same phases.

To manufacture complex **API** (Active Pharmaceutical Ingredient) molecule for a "competitive generic market," most often a creative and newer process must be developed which, in reality, constitute a NEW, INNOVATIVE, and especially, SHORTER-PROCESS for to be economically viable for competing with the Brands at70%-80% lower cost. For complex APIs, **this stage of development includes the development of the total synthesis at the lab scale, delivery of the proof of concept sample, analytical developments, several scale-ups, and finally, validation of the manufacturing process. Such operation depending on the complexity of the API, may take 1-3 years and about $ 1-1.5 M of investment.**
Stage 2.
To commercialize the API, it is necessary to follow the **FDA Generic Office** guidelines, which implies the completion of the **Drug Master File (DMF)** registration according to the FDA guidelines and regulations.
Our experience with *three* generic products that we have developed (and some still are in developments phases) has led us to conclude that while the **stage 1** could be (and should be) completed by innovative startups and small businesses, **Stage 2** requires Government's help and assistance similar to what has-justly-been anticipated in phase 2 of the SBIR program for new drug developments and commercialization.
There are reasons for this.
The scale of operation and the strict requirement of following the FDA guidelines dictate the size of investment for covering the manufacturing of at least three (more likely 4) batches of the API. FDA instructs that manufacturing to be carried out at specific scales which are determined by the commercial quantity of the API. The production process ought to be done at an FDA approved cGMP facility. The operation required extensive analytical method developments & validations, substantial paper works, and regulatory oversights & controls. To these expenses, we must also

add the cost of registration of the Drug Master File with the FDA. No startup is equipped to complete all these pieces by itself. They need to be outsourced to a qualified CDMO facility with the right equipment and experience. The average budget for stage 1&2 for complex molecules, in our estimate, is $ 1-2 M.

Stage 3.
In transforming the API (drug substance) to the "drug product" and entering the generic market, the marketing partner (the Generic Pharma) traditionally assumes the control and bear the cost **of the FDA review and approval, packaging, and distribution of the generic drug**. To our best assessment, completion of the two stages 1 & 2 consumes almost 80% of the total budget that is needed to bring a generic drug to the market. Therefore, it is not surprising that if DMF for an API is available, many generic pharmaceuticals enthusiastically will be ready to invest and go through the third stage of the commercialization phase.
In the early days of Generic drug development (1995-2005) following passing Hatch-Waxman Act, 1984, act, many Generic Pharmaceuticals would fund the phase 2 development of the generics. However, following the surge of merger & acquisition and more stringent FDA guidelines for efficacy and safety of the generic drugs (following Heparin adulteration in 2008 and death of 80 patients) funding for Generics Developments with low revenue of <$300-500 M has dramatically decreased to almost none.
The response we have received from a few generic Pharmaceuticals that are currently populating the generic arena with no exception has been:

"In the end, we concluded that the project would not be the right fit for our U.S. business. … ultimately did not reconcile with the ***cost of the project*** *and* ***the size of the innovator market****".*
In simple words, "it is not profitable enough for us."
[FYI, this particular response was for a breast cancer chemotherapeutic drug with $340 M sales worldwide]

For innovator drugs with sales over $500 M, we are facing with other tactics such as Generic monopoly and duopoly that are currently maintaining the Generic price at about 80-90% of the Brands! There are other tactics, as well. Recently it has been discovered and reported that the price of the Brands was increased several times just before the generic came out, as seen in the graph below for the Nitrostat, a heart medication made by Pfizer. The drug's price had been increasing for years, but there was a significant jump of about 56% in 2015, the year before a generic version came on the market, according to the report.

In summary, we believe by incorporating "GENERIC SBIR" in the SPID ACT of 1982, we will be creating the right environment for many pharmaceutical entrepreneurs and startups to invest and create a new wave of Generic Developers/ Manufacturers/Marketers/Distributors. The participation of both *SBA & FDA Generic offices* would tremendously help the Generic manufacturers to overcome the high barrier of the completion & submission of the generic drug "DMF" and pave the road for a smarter Generic market.