Sometimes Less is More

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Last month I talked a bit about the impact that the changing political winds might have on capital flows and investments, which of course eventually leads to stock prices. Just to reiterate, I am an unapologetic capitalist, so when I see U.S. presidential candidates speaking in earnest about "democratic socialism" and people seem to be paying attention, it raises my draconian senses. Certainly, one of the higher profile areas of debate is of course healthcare, which many recent polls have identified as *the* hot button issue for the current election cycle. Given the breadth of the issue, that is not surprising, after all, it is an issue that touches a greater portion of the electorate than most, it makes up an increasing portion of overall GDP, employment etc. and as I noted last month the industry is a mass of complexities that make solutions illusive.

One of the issues I have been harping on as of late is the idea that those pushing for greater controls on the industry need to be careful what they wish for and perhaps nowhere is that notion more cogent than with pharmaceutical prices. Touching on a few of the high-level arguments, anyone who pays for prescriptions can attest that they seem to be getting more expensive, and that recognition is probably enhanced by higher overall deductibles (another growing pain point for consumers), which tend to bring those prices to the forefront especially for patients paying for prescriptions out of pocket (for instance) prior to meeting deductibles. One does not need to listen to much of the political drumbeat to ascertain that drug pricing is in the sights of liberal politicians but are also not lost on conservatives. The only difference seems to be who to blame. For those on the left, the blame lies with greedy market players (pharma, insurers, pharmacy benefit managers etc.), while those of us on the right prefer to sight single payer healthcare systems around the world that are essentially being subsidized by U.S. consumers for what is largely U.S. pharmaceutical innovation. As with most of these disagreements, there is probably some truth in each of these views although again, given the complexities, finding the "truth" and in turn optimal solutions, is no simple task.

While again, I do believe there is good reason to believe that the U.S does in fact subsidize the world's pharmaceutical demand, I also think some of the problems with the U.S. healthcare system have to do with additional nuances as well. For starters, healthcare at least acute healthcare, is unlike nearly every other product or service on earth. Succinctly, if a person is dying of cancer and the only potential cure is a particular therapy, their demand for that product is largely inelastic. That is, they will demand the therapy/product regardless of its price. Oddly enough, for any patient who has health insurance in one form or another, the perfect inelasticity of that demand is compromised by the fact that the entity paying for (much of) that therapy is not the patient. That is, the payer may have a different view of that elasticity than the patient. That dichotomy tells us a bit about the rising cost of healthcare or at least the rising cost of pharmaceuticals and that may have some implications for biopharmaceuticals and medical devices as we move forward, especially small emerging ones.

As many biotech/biopharma investors will attest, the FDA approval process is long and expensive. According to www.Policymed.com, *"Developing a new prescription medicine that gains marketing*

approval is estimated to cost drugmakers $2.6 billion according to a recent study by Tufts Center for the Study of Drug Development and published in the Journal of Health Economics. This is up from $802 million in 2003—equal to approximately $1 billion in 2013 dollars, and thus a 145 percent increase in the ten year study gap. Furthermore, while the average time it takes to bring a drug through clinical trials has decreased, the rate of success has gone down by almost half, to just 12 percent". To some that fact may not justify the extraordinary cost of many new life saving pharmaceuticals, but certainly explains the basis. On the other hand, while again many investors in the space may lament the long approval process, the fact is, while development costs have continued to increase, review times have decreased quite dramatically over the past few decades. By the way there are reasons for that, which also carry their own set of nuances.

Thalidomide was developed in Germany in the late 1950's, to treat a variety of things including morning sickness. The short story is that it was later discovered to cause birth defects in some children whose mothers used the drug. While the U.S. FDA refused to approve the drug at the time, the ill effects of the drug across the world caused many international drug agencies to develop and implement more stringent requirement for testing both the safety and efficacy of new drugs. In the U.S, as a result of those new approval layers, review times at the FDA continue to increase through the 1970's, and by the end of that decade stood at *nearly 3 years.* Public outcry of the FDA's lengthy review process began to accelerate through the 1980's, which coincided with the spread of HIV. Specifically, patient advocacy groups began suggesting (and protesting) the notion that the FDA was perhaps purposely holding back research and potential cures for the virus. (Just to be clear, at the time there was pressure from constituencies like investors and drug developers with respect to other diseases as well, although HIV was quite topical).

As a result of some of the public outcry and/or recognition by the agency and lawmakers that the lengthy review periods might be keeping lifesaving therapies from patients, in 1992 the federal government passed the Prescription Drug User Fee Act. The legislation provided for the funding of FDA review staff via fees paid by companies presenting therapies for approval. In exchange, the FDA committed to reducing review times to 12 months. That law was reauthorized in 1997 reducing review times to 10 months, and in 2012 (along with fast track designations which were actually created in 1988) the FDA created a new "breakthrough therapy" designation for drugs which demonstrate promise on their own or in combination with other drugs that show a measurable improvement from current standards of care. To translate, the designation was designed to provide patients, who had tried and failed existing standard therapies, access to new drugs that might potentially help them. Over the past 30 years, the FDA has streamlined the review process significantly, (in part with funds primarily from "Big Pharma", which some view as a conflict) and that posture has led to more drug applications, more "breakthrough" designations and ultimately more drug approvals. That brings us to my point of concern.

In my view the scrutiny over elevated/rising drug prices in the U.S. is not going away. In fact, they may become front and center regardless of election outcomes, because we have seen concern from both sides of the political spectrum and the weight of high drug prices is becoming untenable. At the same time, more drugs are being developed. For instance, on the cancer front we are seeing successful drugs like Keytruda expanding into additional indications, but also attracting trials in conjunction with other (non-approved) drugs. In most instances, those potential "break-through" therapies might ultimately be used in addition to Keytruda, which already carries a price tag of about $150,000 per patient. So presumably, upon approval of some of these breakthrough drugs, a patient may require $150,000 worth of Keytruda as well as another large sum for the new drug in conjunction, which may collectively still fail. That begs the question, at what point will the sum of these combinations become too much for the systems to bear? Further, as we have already seen with many drugs treating the same illness, the markets for these drugs regardless of pricing *are finite*. Put another way, even as some drugs achieve approval, there is no guarantee they will be

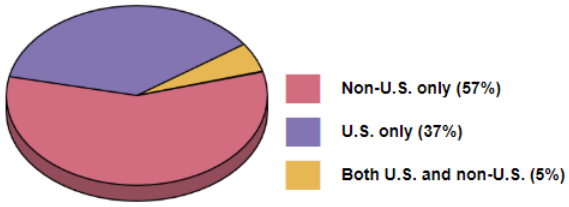
successful in the market, which may become a function of price, improved patient outcomes vis-à-vis existing standards of care and ultimately the adoption of these therapies by relevant industry players like physicians and payers.

The chart below from www.ClinicalTrials.gov reflects the size of the clinical trial environment. As you can see, there are many of them going on:

The chart below shows the distribution of locations for recruiting studies registered on ClinicalTrials.gov.

Percentage of Recruiting Studies by Location (as of June 17, 2019)

Total of 50,854 recruiting studies



Location	Number of Recruiting Studies and Percentage of Total (as of June 17, 2019)
Non-U.S. only	29,193 (57%)
U.S. only	18,842 (37%)
Both U.S. and non-U.S.	2,707 (5%)
Not provided	112 (0%)
Total	50,854 (100%)

While the above seem like a large number, I submit, according to a recent study from MIT, only *"14 percent of all drugs in clinical trials eventually win approval from the FDA. Approval rates ranged from a high of 33.4 percent in vaccines for infectious diseases to 3.4 percent for investigational cancer treatments".* Most biotech investors are well aware of these statistics, although, this number is higher than it was once believed to be (closer to 10%). I suspect that higher success rate might have something to do with the fact that the FDA seems to be approving more drugs and approving them faster than in the past, and again, that may have something to do with the pressures put on them to do so from various constituencies. That brings me to my final point.

There are some who believe the FDA is approving too many drugs too quickly without the benefit of more scrutiny. Many of those in that camp also believe the reason for that ties back to the 1992 law I referenced above, which provided for companies submitting reviews to pay for the salaries of the reviewers. I think most would agree that while not necessarily telling, it is a legitimate concern. That notion leads to two potentially negative outcomes, which essentially makeup the framework of clinical trials in the first place and the first is safety.

Obviously, the worst-case scenario from an FDA process that is not thorough enough is the thalidomide example, where patients taking an approved drug end up worse off for taking it. That is, the cure becomes worse than the disease. Of course, in some instances, and the "breakthrough" designation is probably a good example, that notion sometimes gets overruled by the fact that the patients are already quite sick and have run out of other options. That is, they are willing to "take a chance" on the potential side effects of a

drug that could help them because their prognosis is dire without it. Even with safety concerns considered, what do they have to lose? On the other hand, the second question is, "does the drug work"? One of the problems with fast tracking drugs, is that there is less time spent evaluating the longer-term impact of drugs on patients, and that includes *safety and efficacy*. Again, I suspect that stems from a willingness of very sick people to try anything that might help them no matter how remote the possibilities of success. The trouble is, while terminally ill patients may be willing to try therapies with long shot odds, the entities that must pay for those therapies may not be willing to pay for those high-priced offerings with limited chances of success. At some point in time, all healthcare systems have to draw the line in terms of what they will pay for and what they will not, and a drug's expected success rate, especially relative to other existing (more proven and probably cheaper) standards of care, will play a large role in determining that willingness. I would argue that on the face, one of the bigger differences between single payer healthcare systems and multiple payer (private insurance) systems like we have in the U.S. may be the willingness of those systems to broaden the scope of therapies they make available to their covered lives. While I applaud the systems, enterprises, and the people engaged in trying to find new/better therapies every day, there are economic limits to what can reasonably be provided and I think the growing burden of healthcare costs are beginning to lead to more hard choices about who gets what in terms of treatments. Again, that notion will likely impact the success of new drugs and/or devices **even beyond** their success in obtaining FDA and other similar international approvals.

https://www.pbs.org/newshour/health/fda-increasingly-approves-drugs-without-conclusive-proof-they-work

file:///C:/Users/amian/Downloads/tayteo_2019_oi_180285.pdf

https://blogs.sciencemag.org/pipeline/archives/2018/02/02/a-new-look-at-clinical-success-rates

https://www.centerwatch.com/cwweekly/2018/02/05/new-mit-study-puts-clinical-research-success-rate-14-percent/