One Important Lesson from Biogen's Surprise Announcement on Hopes for an Alzheimer's Drug: A Commentary

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1. Potentially Good News for Alzheimer's Disease Patients

Alzheimer's disease patients recently received hopeful news in late October 2019 upon hearing a public announcement from Biogen Inc. that its experimental drug aducanumab did work in certain patients who received the highest dose for a longer period in one particular clinical study (ENGAGE) after further post-hoc analysis supporting findings from the EMERGE study.[1-2] Biogen earlier stopped a collection of late-stage clinical studies (EMERGE and ENGAGE) on the drug because of disappointing results according to initial analysis.[2] Later analysis demonstrated that certain patients might receive benefits from the drug, through exhibiting less cognitive decline as compared to placebo, based on biomarkers or genetic variants.[3] Biogen announced it will seek approval of aducanumab from the FDA in early 2020 while continuing talks with regulators in various international developed-country markets.[1] The experimental drug targets beta-amyloid proteins that form plaque in the brain, a condition thought by researchers to advance the disease.[3] If approved by the FDA, the drug could become the first treatment to slow the progression of Alzheimer's disease in patients.[3] One challenge will be the possibility of a drug, potentially benefitting millions of patients in the US (estimated at 5 million) and worldwide (estimated at nearly 50 million),[4] and the added cost pressures it will place on healthcare reimbursement mechanisms given the lack of available effective treatments.[1] Other challenges involve overcoming mixed results from the two clinical studies, the FDA may want to see additional evidence to establish clarity around the true benefits of the drug, and continued safety concerns regarding the rate of a brain swelling side effect among patients in the high-dose group.[5]

2. One Important Lesson from Biogen's Announcement on this Potential Breakthrough

There are many lessons one could take from Biogen's announcement. The authors here wish to emphasize one very important lesson, as noted in previously published white papers on the Axtria Research Hub (https://www.axtria.com/axtria-research-hub-pharmaceutical-industry/). Generating novel medicines to combat complex and lethal diseases is risky, costly, and takes time. Incentives are needed by pharma companies to leverage advancements in basic science to develop these medicines. The effect of recent policies promoted by politicians in Washington on drug pricing, if enacted, threatens to undermine future pharma innovation that will ultimately work to the detriment of patient health. The Trump administration's support for the International Pricing Index (IPI) scheme imposed on Medicare Part B drugs is already having adverse consequences on companies with significant revenue exposure through this channel.[6] Reactions from pharmaceutical and biotech industry trade organizations were swift and critical, noting adverse consequences to future R&D investment and effects on patients.[7-8] The importation of drug prices into the US from countries that have socialized healthcare systems is just another form of a price control imposed on pharma companies. There are numerous and devastatingly onerous pricing bills under discussion in Congress, such as a bill

from Speaker Nancy Pelosi (HR 3), which is gaining traction among politicians looking for cover with the upcoming 2020 elections, to be seen taking on pharmaceutical companies.[9] There are discussions about the importation of drugs among various states, with surprisingly tacit approval from the Trump administration.[10] Again, such schemes merely represent another form of a price control with the same adverse effects on investments in R&D, diffusion of new drug technology, and detrimental effects on future patient health outcomes. There is also growing support for health technology assessments (HTAs) and the Institute for Clinical and Economic Review (ICERs) to implement value-based frameworks to evaluate the prices of new therapeutics. Europe already applies such frameworks, such as the National Institute for Health and Care Excellence (NICE) used in the UK. The concept of value-based HTAs is worthy from a societal policy standpoint and to guide pharma companies on what health and economic endpoints they must reach to launch drugs, but so long as HTAs do not turn into mechanisms solely for the purpose to impose cost controls on drug pricing.

The preceding pricing policies represent a direct existential threat to the pharma industry. The case here illustrated by Biogen's continued efforts to find a meaningful benefit to treat a devastating and costly disease clearly demonstrates a known maxim in the industry – the quest to find effective treatments for increasingly challenging diseases involves high risk, uncertainty, and cost to develop new drug innovation.[11] The targets now selected by pharma companies for development often involve more lethal and/or rare diseases for which no good options currently exist, and where the mechanism of approach entails more complex drugs such as large molecule biologic and genomic-based treatments instead of small molecule drugs.[12-13] Almost half of all US drug spending is on specialty medicines, with new anti-cancer drugs representing the largest focus by pharma companies, with 57 oncology new active substances (NAS) launched out of a total of 219 in the last five years.[13] While many disease areas have seen new drug development, especially with the applications of better basic scientific/biological information and new mechanisms and/or technology to deliver medicine, many pharma companies have left trying to find effective treatments for Alzheimer's.[3] More than 120 drug therapies for Alzheimer's have failed.[3] The imposition of drug price controls, in various forms, will stifle future drug R&D and adversely affect the diffusion and access of new novel medicines to patients consistent with economic theory and actual industry evidence.

Outside the US, many countries use socialized healthcare systems and direct governmental price controls to deal with lowering the price of drugs, with unintended negative consequences and illusory benefits to patients. The US takes a more balanced approach to the drug pricing problem. The US tries to balance the needs of innovators to have economic incentives to compensate them for the high risk and cost of drug development via patents with a limited duration that protect company intellectual property while providing other governmental subsidies and accelerated approval processes to promote new drug innovation that could benefit patients. At the same time, to diminish the monopoly effects on pricing caused by erecting patents, legal frameworks have been erected to allow for the expedited entry of generic and biosimilar drugs once patents expire, bringing drug prices down, increasing drug access to patients, and thus improving health outcomes and potentially lowering overall treatment spending. The US tradeoff is not perfect from a theoretical economic analysis perspective. However, the practical proof that this approach is better than the social-democratic Canadian or European models shows that the US policy institutional framework facilitates the global engine for new drug development with the fastest rate of diffusion of new drug technology, years ahead of other countries that impose direct price controls as the preferred policy approach. We know from experience and analysis that direct price controls on drugs adversely affect the investment in R&D and stifles the diffusion of new drug technology.[14] A major study of 642 new drugs analyzed over 20 years empirically found that a strong patent system accelerates the diffusion and access of drugs for patients, with similar effects in both high and low-income countries, while countries with price regulation schemes have significant delays in the launch of new drugs.[15] Thus, the consequence to patients is very clear and simply this – what if, for example, you have a rare cancer that needs a novel drug therapy that has been developed or is under development and/or available under an accelerated governmental regulatory approval process? Your chances of longer survival are much better if you live in the US than anywhere else in the world. Period.

3. A Time of Change – What Should Pharma Companies Do?

3.1 New Realization and New Thinking

So, what should pharma companies do? The preceding review and comments demonstrate that the old ways of commercializing drugs by companies are no longer sufficient for generating long-term success, and are not economically sustainable. The current public reactions to pharma pricing practices and proposed blunt policies are a direct consequence of a commercial model design that continues to be volume-based instead of value/outcomes-based. A significant change in thinking is required.

Presented below are our views on a new realization and new thinking that will be required from pharma executives. The first recognition by pharma companies is the increasing importance of analytics as the pharmaceutical industry landscape evolves in multiple ways:

1) *Change in focus from large patient populations to small patient populations.* There has been and will continue to be an ongoing move away from primary care blockbusters toward specialty medicines and treatments for rare diseases.

2) *Resulting in challenges in affordability and pricing.* The affordability of specialty medications is a continuing challenge. There is a much greater emphasis on value generation and the ability to demonstrate superior patient health outcomes. Almost regardless of which political party is in power, pricing pressures continue to rise.

3) *Continuing diffusion (lower physician autonomy) in decision-making around treatment choice and pharmaceutical drug utilization.* There is a greater influence of stakeholders other than physicians in the healthcare continuum, such as institutional providers, payers, and patients.

4) *Continuing change in healthcare provider (HCP) and other stakeholder needs for medical information and in preferences for channels to engage with other than pharma representatives.* HCPs today have a wide range of digital and social media channels available to them to access medical information without going through the pharma industry.

5) *Resulting changes in commercialization paradigms.* These changes are as follows: a) move from extreme dependence on personal selling to multi-channel, to orchestrated omni-channel promotion; b) increased importance of account management roles; c) increased importance of digital marketing for both HCPs and patients; d) increased complexity in messaging and need for precision targeting in specialty; and, e) increased importance in medical affairs as a source of objective and peer-to-peer delivered scientific, medical and clinical information.

The second recognition by pharma companies is the existence of new capabilities for data-driven decision-making will be increasingly important in this era of change. There is much greater promise today for better data-driven decision-making because of the following factors and trends:

1) Data proliferation. Patient data sources are rapidly expanding, such as diagnostic data, claims data, electronic health records, wearable personal data, and Internet of Things (IoT) data.

2) Advances in big data analytics and technology are making it much easier than in the past to bring the best data and insights to the point of decision.

3) Analytics is becoming much more accepted and prevalent across the enterprise.

4) Services are being replaced by software and platforms – on one hand delivering automation and efficiency, and on the other, facilitating more effective decision-making at all levels in the organization by leveraging machine learning (ML) / artificial intelligence (AI) and other algorithms.

5) The right combination of algorithms, platforms, and business decision-making processes is driving recommendations across the enterprise, for large and small decisions. This is enabling stronger linkages between strategy and tactics than organizations have historically enjoyed.

6) More stakeholders and decision-makers than ever before are data literate. There is a growing ask for multiple parts of the enterprise to be able to access the power of data and analytics directly, rather than relying on siloed analytics groups or external partners.

7) In several other industries, corporations have made giant strides in leveraging data-driven ML/AI in a myriad of business processes. Pharma executives are in turn asking whether we as an industry are fully leveraging the power of ML/AI and enabling competitive capabilities for tomorrow.

All of this has led to incredible buzz around analytics. How much of this is a true opportunity vs. hype? The next subsection will discuss what recommendations pharma executives should initially undertake in order to stay competitive in this time of change.

3.2 Recommendations of What Pharma Executives Should Initially Do

The following recommendations represent a short non-exhaustive list of what pharma executives must initially do in this time of change and in response to the existential threat current pricing proposals pose to the industry.

1) *Create a value/outcomes-based commercial model design (CMD).* There will be increasing pressure on pharma companies to move away from the current volume-based CMD to a value/outcomes-based CMDs as the healthcare system places greater need on evidence-based medicine to demonstrate value and thus empirical support for higher prices of specialty medicines. Such a shift will dramatically affect all aspects of sales, marketing, payer/managed markets, and commercial strategy and operations.

2) *Integrate health economics and outcomes research (HEOR), real world evidence (RWE), market access services / CMD analyses for the evolving pharma marketplace.* Performance-based contracts and HTAs will become the norm, where HEOR and RWE analyses will be needed to support value/outcomes-based institutional frameworks.

3) *Reorganize the structure of the commercial organization by breaking down traditional silos that inhibit interdisciplinary thinking.* The business problems tomorrow facing pharma executives will require interdisciplinary thinking not only across traditional siloed commercial departments but also with clinical, HEOR, and RWE teams. Such reorganization will be required to develop holistic solutions to support a value/outcomes-based model design.

4) *Develop a commercialization strategy specific to oncology.* Pharma companies are increasingly focusing their R&D portfolios and long-term business strategy in oncology.[16] The commercial model for oncology is more based on disseminating scientific/clinical/medical information than what is seen in the traditional "reach-frequency" approach. This means developing a framework on how an oncology CMD affects the applications of decision science, commercial operations, and cloud information management for starters.

5) *Understand both the opportunities and challenges for the successful commercialization of orphan drugs (ODs) for rare diseases (RDs).*[12] The referenced white paper lays out in detail how the commercialization of ODs for RDs requires a range of strategic and tactical elements to implement from pharma companies that differ from other drugs. The commercialization elements are listed in approximate chronological order according to the life-cycle of the project/product, from the clinical trial stage through to post-launch:[12]

   a) Development of patients for RD clinical trials.
   b) Improvement in RD diagnosis and treatment.
   c) Market access and patient affordability.
   d) Pre-launch preparations.
   e) Sales and marketing activities.
   f) Specialized supply chain development.
   g) Engagement with governmental agencies and policy decisionmakers.
   h) Greater cross-functional collaboration within the pharma company.

6) *Invest in new analytical capabilities, platforms, and data structures to support a value/outcomes-based CMD.* A value/outcomes-based CMD will require going beyond traditional econometric analyses for promotion-response modeling, to methods like propensity scoring models used in biostatistical analyses, optimization/simulation/prediction modeling, ML/AI platforms, Next Best Action (NBA), trigger and real-time analyses, augment existing physician-level databases at the patient-level capturing health outcomes and cost of treatment (e.g., claims data, electronic health records, etc.), digital and social media, and develop the capability to link all of these databases to form a more complete picture of the patient journey, treatment, and outcomes.

7) *Focus on developing novel pricing models to support the upcoming generation of specialty medicines.* The IQVIA Institute for Human Data Science provided ominous pricing scenarios and their effect on US drug prices and spending trends.[13] For example, the launch of gene therapy one-time treatments, and the controversy around the pricing of Zolgensma® [17-19] (there exist around 300 similar gene or cell therapy one-time treatments in development), will place added cost pressures on reimbursement systems not designed for such drugs.[20] The pricing of new novel medicines will come under extraordinary scrutiny and pressure unless new approaches are devised. Interestingly, HEOR models that assess cost-effectiveness support the pricing of Zolgensma® despite public criticisms over the pricing of the drug.

4. Conclusions

The announcement of Biogen's potential breakthrough in finding a drug that may finally deliver benefits to Alzheimer's patients represents a milestone in treating this dreadful disease. It also should serve as a reminder to those who wish to undermine this engine of innovation what it takes to bring novel medicines to the marketplace. As Milton Friedman, Nobel Prize-winning economist, famously said, "There's no such thing as a free lunch." Unfortunately, a rational pharmaceutical policy that is needed to maintain innovation for the benefit of patients is in short supply among our politicians. The prospect of seriously onerous policies against the industry is no longer theoretical but now a distinct possibility. It is no longer "if" but "when" such policies will occur. Pharma executives must be prepared to shift their thinking and operations when such policies are put into effect. This white paper lays out the reasons for these changes and action steps executives must make to shift from a current volume-based to value/outcomes-based CMD. Few pharmaceutical consulting companies have the expertise in all the aspects, like Axtria, needed for executives to have a strategic and operational partner to work through the required changes.

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