2014

The Drug Development and Business of Traumatic Brain Injury

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THE DRUG DEVELOPMENT AND BUSINESS
OF TRAUMATIC BRAIN INJURY

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An Honors Thesis submitted to the
Department of Management
in partial fulfilment of the
requirements for graduation with
Honors in the Major.

Degree Awarded:
Spring, 2014
The members of the Defense Committee approve the thesis of Ryan T. Kearney defended on April 17, 2014.

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This thesis is dedicated to my friends, family, and professors. Without your continued guidance and support, I would not be where I am today. I thank each of you for being the wheels that keep my wagon rolling. I love you guys.
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I. Introduction

If you are a scientist developing a pharmaceutical drug or if you are a member of the development team, settle in because this is the trip for you. This story and insight will take you along the path for the development and formation of a company around a concussion-treating drug. This story covers what the drug is, how it was developed, the pitfalls and successes that were navigated, and where the company and team reside today. While this is a true story of the success and improvement of treatment for a leading health condition, there are many areas that could have been navigated differently if you are planning to take yourself down a similar path.

II. Background

One of the most common injuries incurred by a human is mild Traumatic Brain Injury (mTBI). This is most often referred to as a cerebral concussion. Environmental conditions that cause concussion are falls, vehicular accidents, military work, and different athletic sports. A concussion occurs when one’s head strikes an object or is hit by another force; with it normally being a violent, jarring motion. These don't always result in concussions but when enough force is applied in the correct area, a concussion normally results (Heller, 2013). Scientifically, it is known as a loss of consciousness and related traumatic amnesia that has occurred as a consequence of head trauma in the absence of physical damage to the cerebrum and other parts. Also, this clinical syndrome is characterized by direct and momentary impairment of neural function such as disturbance of vision, alteration of consciousness, equilibrium, etc. due to forces applied to the brain (Ommaya and Gennarelli, 1974). Treatments of these injuries are normally a visit to the hospital depending on the severity. Some people tend to shy away from this visit, but even if it seems to be rather mild and not too serious, significant problems can arise that were a result of this injury. Currently the most prescribed treatment is strictly rest. Obviously, stay out of physical activity such as one’s sport is a given. Nevertheless, what many people do not realize is that tasks that require thinking such as reading or watching an intriguing movie can over stimulate the brain while it is trying to repair. Also, it is strongly advised to avoid bright lights and loud sounds as often as possible when in recovery.

To understand why recovery is so important and why certain activities can produce greater problems, one must understand the inner workings of the brain. The brain is composed of neurons that communicate between each other through axons and dendrites which can be thought of as branches connecting one neuron to another. These neurons are in fact human cells but are immensely different not only in their function but most importantly in their ability to divide into more cells. To clarify, if one can imagine how their body heals; one can see new cells consistently regenerating and reproducing to heal wounds. The brain neurons unfortunately do not work this way; they do not reproduce regularly. Neural Growth Factor (NGF) can help with the
reproduction, but often NGF is not produced in a mTBI. When a concussion occurs, the brain is essentially bruised similar to what one would receive after bumping their shin into a coffee table. This swelling also occurs in the brain, and if not given enough time to properly heal, some neurons will end up dying off. This effect has a direct correlation to people with multiple concussions having trouble thinking, speaking, and recalling memories because the inter-workings of the neurons cannot find certain memories or specific functions can’t travel through the synapse’s to achieve an effect.

Considering the medical significance of this injury and the prevalence of its occurrence, it is clear that the business of concussion presents a huge opportunity. As with any business, one needs to address their market. With approximately seven billion people on this planet, and all having brains, there are potentially seven billion customers. From an investment perspective, this market is incredibly attractive. Since this injury can occur in any human and can also occur at any time, treatment of mTBI has nearly incalculable potential. There can also be multiple treatments for an individual because there is no limit on how many mTBI one can experience. Due to this fact, it is surprising at first why not many companies have focused on a cure/treatment to this injury. As mentioned before, the primary standard of care and treatment has been strictly rest.

III. Prevasol, the Candidate

For Prevacus, knowing the background of concussion and treatment, they created a drug to address and treat concussion. The drug is a neurosteroid administered through the nasal cavity. It’s administered this way for two reasons. The first reason is for the ease of application on the playing field or the field of battle. The second reason is the patient will get more of the drug directly into the brain with higher concentration without ever entering the blood stream, thus reducing the potential systemic side effects of the drug. Animal experiments have shown that Prevasol is equally effective as other neurosteroids in reducing cell death, brain swelling, and inflammation, and it also has three times the antioxidant activity of all others, which provides an added protective benefit when treating concussion a known condition for increased oxidative stress secondary to a cerebral energy crisis (Prevacus).

The drug works to shield the brain prior to injury and reduce the pathology associated with post- injury symptoms such as memory impairment and imbalance. Prevasol is lipophilic or hydrophobic, meaning it can easily cross the blood-brain barrier and simultaneously eliminate swelling, oxidative stress, and inflammation of the brain. Based on their pre-clinical findings, Prevasol activates a receptor in the brain that leads to the production of export water channels, anti-oxidants, and anti-inflammatories simultaneously.
IV. The Competitors

While there isn't any approved competition because no drug has been given the go ahead by the Food and Drug Administration (FDA), there are alternative options. One of these options, progesterone, has already been mentioned above. This is a viable treatment, however, its' side effects for mTBI may be more harmful than the actual effects on healing the drug offers. An alternative option is Neuren pharmaceuticals, NNZ-2566 (Neuren Pharma). This drug has been shown to have multi-faceted actions which significantly reduce both inflammation and apoptosis (cell death), protecting the neurons and their surrounding infrastructure. It is known that this drug is working with the US Army Walter Reed Army Institute of Research and is in clinical development at the stage of Phase 2 testing for more severe TBI.

V. Why Concussion

The reason for this specific development came from an incident during the time of 1995. Jake VanLandingham was assaulted and had three hemorrhages to his brain from the accident. From this accident, Jake's life had turned upside down. Everything had changed; his memory was severely impaired and smell was nothing but a dream. After struggling with short term amnesia and other related problems, his memory seemed to come back about a year and a half after the incident. With his memory back, Jake pursued a degree in physical therapy with a concentration on neuro-physical therapy. After working with patients with significant brain injuries and birth defects, Jake decided that he was going to go back to do research to get into translational medicine. This was partially because he wanted to help kids like the ones he worked with and because he himself had effects with neurological impairment. Translational medicine is a discipline within biomedical and public health research that aims to improve the health of individuals and the community by “translating” bench-science findings into diagnostic tools, medicines, procedures, policies and education.

Jake had got accepted into the neuroscience program in August of 1999 at Florida State University. This program had three departments associated with it; Psychology, Biology, and the Department of Nutrition, Food, and Exercise Sciences. His principal investigator was Cathy Levenson, who had a PhD in Nutrition, and the major focus of her lab was to look at trace metals in neurodegenerative disorders. These models mimicked Alzheimer’s and Parkinson’s disease. They looked at models of how the nerves were actually dying and what they could do to protect them. They had a special model for copper toxicity and how it looked different over time and the effects that copper had. It took Jake four years to complete his PhD. Within the last year and a half, his work was focused on micro-array where they looked at gene expression in conditions where it was altered from depression and anxiety. Specifically, they looked at the hippocampus where the memory centers are and looked at the olfactory bulb which ties into depression and anxiety in Parkinson’s and Alzheimer’s disease. His PhD thesis
was on the role that trace metals had in neuronal gene expression. He looked at how the trace metals affected the gene expression in models of Parkinson’s, Alzheimer’s, and Wilson's disease. He then was a second author on a paper towards the end of his PhD work that focused on research that used a penetrating brain injury model to evaluate the role of zinc as a neuroprotectant.

Knowing his personal history in brain injury and that he came back to get a PhD to do drug development via translational medicine, he decided to do a post-doctoral fellowship at Emory University in Atlanta working with Donald Stein, Ph.D. and David Wright, M.D.. He worked as a postdoctoral student and then got promoted to assistant director of the Brain Research Lab, the largest lab in the Department of Emergency Medicine. They tried to understand the mechanisms in which progesterone worked and its effects in treating moderate to severe brain injuries in animals. Plus, he looked at clinical blood samples that were coming out of the use of progesterone in brain injured humans. Most of these patients came into the hospital in a coma. These studies took place in 2001, 03, 04, 05, and 06. During that time, they had completed Phase 1 and Phase 2 clinical trials for progesterone in treatment of moderate to severe brain injury. When he was leaving there was a transition to find the funding they needed for a Phase 3 clinical trial.

VI. How the Drug was Developed

In 2006, Jake moved back to Tallahassee, Florida to teach at the FSU College of Medicine in which he was a course director for Clinical Microanatomy. It was a pre-pathological course to help students to start understanding what normal mechanisms of the cellular level look like, compared to what they look like when they go awry when pathology sets in. He still had a little NIH money that he had got from Emory on a drug that never panned out. However, for those first two years he pretty much spent his time getting the curriculum set up for that course. He had to know what the students felt about the course, and how to gauge with other professors on his course with their courses to avoid needless overlap and synchronize the materials being taught.

When he did get back into the lab in 2008, they started working on a concussion model in rats. Typically with brain injury models, one opens the skull up and one would have a direct perpendicular line of the impactor that goes 2-3 mm deep into the brain and causes an injury. They typically have done frontal lobe injuries but there’s multiple spots that one can impel the brain to get different behaviorally responses. Ultimately when one hits the brain, the subject will get some memory impairment, which is one of the main things they wanted to look at because it creates amnesia. When they created the concussion model, not only does the head have to be hit and accelerate and decelerate, but the head has to rotate. This is to get the banging of the cells inside the skull but it also gives a “slinky” type of effect. Specifically, as the front part of the brain moves forward in the acceleration of the head, the back part of the brain lags and everything in between get stretched. This can cause an injury, but not that significant of
an injury unless one also rotates the head during this acceleration and receives a sort of towel ringing thus inducing torque on the brain while it is being stretched. So this stretch and torque combination of acceleration and rotation of the brain and how the brain interacts inside the skull is similar to what they wanted to get for concussion type of symptoms such as balance and memory impairment.

They had to create a closed head injury model where they hit the skull and caused acceleration of the head but at the same time causing the head to rotate. To achieve this, they put the animals in a stereotactic apparatus to stabilize the seventh and sixth cervical vertebrae so one would still get plenty of rotation of the head. They laid the head of the rat on a foam pad and came down with an impacter, but instead of perpendicular to the skull, they came down at a 15° angle giving an ample amount of acceleration but also allowed the head and neck to rotate at the same time to produce the needed torque. This all worked out well, but one of the bigger problems they had early on was that they were hitting the rats in a closed head injury model to get enough acceleration to give concussive symptoms, so they actually had to hit the skull at 6.65 m/s. They had to ensure that at that speed they didn’t break the skull or crack it because obviously if they split the skull they get pieces of the skull in the brain and now they have more of a severe injury instead of the mild. To fix this, they glued a 1 mm thick rubber disc to the skull in order to dissipate enough of the energy from the hit that it would not crack the skull.

The measures of that experiment originally were for memory impairment. In addition, they did diffusion tensor imaging with huge magnets to study the effects from the stretching and torque. They were able to show that it was breaking axonal tracks between different areas of the brain; specifically between the frontal portion of the brain were the impacter came down and on the same side and opposite side of the temporal regions where the memory centers were held. From this, they were able to show that their model caused memory impairment and morphologically the tracks that they were damaging from this model linked straight into the memory centers of the brain.

The results showed that this impact in a rat led to memory impairment for about 36 hours and they showed some signs of balance impairment. Now they began to think about this mild brain injury concussion model, what would be some of the neuroprotective drugs that may be given to the animal to prevent this memory and balance impairment? For this, they went back and dove into neuroprotective receptors on experiments Jake did at Emory and looked at the mirror image, or enantiomer, for progesterone which did not bind the classical progesterone receptor and therefore would have less side effects. For instance, he knew the mirror image did not have the infertility and the blood clotting that came along with continuous progesterone administration. Yet, it still stood to be neuroprotective. In 2011, after two years of more research, they put in the use patent for the enantiomer of progesterone for mild traumatic brain injury.
There actually weren't any direct patents for the use of progesterone on concussion. The whole goal was to look at concussion as a 30 day problem. Some people get better in two weeks and some have problems for years. Most of all, they knew that after 30 days if one was still having problems, they were probably going to have lingering effects for months or years. What they wanted to be able to do was to have a treatment that can be used for up to 30 days, to prevent what is called post concussion syndrome or similar concussive symptoms that you had acutely that seem to linger beyond 30 days. They wanted to have a drug which could manage it for the 30 day period.

VII. Formation of Prevacus

The research team and Jake got into discussions with the Florida Institute for the Commercialization of Public Research with what it may look like to take this new technology and commercialize it. The idea was to get the drug and research out of an academic setting where one is limited with certain lab practices that are required to make a drug and collect data and thus, put it into an environment where one could do the tests where results could be shown to introduce the drug into clinical trials. The Institute gave them a $300,000 matching loan. In the beginning, they helped them make the company into a C-Corporation, helped them find a corporate lawyer, and helped set up restricted stock, common stock, and arrange specific bylaws for regulating the company. Also, they assisted them in acquiring lab space in the Sid Martin Incubator which is a world-renowned incubator in Alachua, Florida. In the meantime, they started fundraising and they had their first fundraising in July 2012. The company had officially been formed in June 2012. In August 2012, the lab actually entered the Sid Martin Biotechnology Incubator. The company had raised $300,000, and the Florida Institute had matched, giving them a total of $600,000 of operating funds to begin drug development.

Nonetheless, a majority of the funding needed to go into developing larger quantities of the drug in order to have the drug to do the research they needed. They had a rather difficult time in picking the right lab. Steroid chemistry is not done in many labs across the world, because there are always concerns when dealing with steroids that are hormones with the lab technicians having engagement with the drug on their health. They ended up choosing Pharmaron Inc., which is an international laboratory set up in Beijing, China. At this time, they did not know it was 25 steps to make the drug which was way too arduous and they needed to get those steps down in order for them to have a drug that was ultimately affordable for the patients. If it cost so much to make the drug, what was the cost that would be responsible of the patient? Plus, knowing that mild dramatic brain injury, 99% of the time, is not a life or death circumstance, one needs to be even more leery of cost control and start working on getting those synthesis steps down.
Their goal was to get it down to 10 to 12 steps. They were fairly successful in getting it down to 17 steps. At this time, when they were getting the synthesis steps down, they started to put in patents in order to protect the process they had. They had the usage patents on the drug for protection against concussion, but now they got into process patents. Process patents are how you make the drug, or the process of it. Those were set up for further protection of the intellectual property of the drug because now they could make it quicker and they owned/protected the steps of which made it quicker. They finally got enough of the drug made to start some animal studies in early 2013. They begin behavioral and molecular studies and they then entered into cell culture models. For these, they determined what the drug looks like to a neuron sitting in a dish compared to what it looks like when the cell is deprived of oxygen and the cells receive the drug.

They continued to see strong, positive effects with the drug, but they could still never get the drug past the reaction step that is called the Birch reaction. This reaction is strenuous and was costly to the making of the drug. Consequently, they hired an organic chemist who had done his PhD at MIT by the name of Dan Levy. Dan had found 18 analogs to the enantiomer and one of the analogs was just the removal of a methyl group. If one removes that methyl group, in theory it wouldn’t change the effects of the drug, and one didn’t have to go through the Birch reaction in the synthesis. Now they had the ability to create a process by removing the methyl group of the enantiomer that would allow them around the Birch reaction. They could make the drug for much cheaper but they had to prove that without that methyl group the drug still worked. They spent a few months doing that and it looked just as good in improving memory, motoric activity, and binding the same affinity to these neuroprotective receptors. This gave them a better patent protection position because now they didn’t have to worry about any type of overlap that Jake had at Emory. Now they actually had a new analog that was theirs, that worked just as good, and that could be made much cheaper.

They moved into mass production of that drug in the fall of 2013. Now they were down to 12 steps. It went from 17 to 12; the key was getting rid of that Birch reaction because even though that was just one step, it took forever and also, it was the only step that had potential toxins that got produced as a result of the drug. The drug was working just as good and they felt like they brought a ton of increased value to the company.

This is currently where they are at; working with this new analog of the enantiomer. They have made enough of that drug to get through Phase 1 clinical trials. They currently are in the step right before Phase 1 clinical trials which is called toxicology. This is where they are using that drug in high concentrations in animals to see if there are any toxic effects. Basically everything is toxic at a high enough dose. Even water’s toxic at a certain level. However, they need to know how high they can go before it’s toxic and compare that level to the efficacious level to make sure that they have a big enough gap between those two so they feel comfortable entering into Phase 1
clinical trials, giving this drug to humans. These trials will be done on normal subjects, with the goal that when Phase 2 starts, they will have a smaller group of patients that have had a concussion that will get the drug at first, being Phase 2A. They will then go to a larger group of patients in Phase 2B to show the efficacy of the drug. Once toxicology gets close to completion they will have a pre-IND meeting with the FDA.

VIII. The Phases of Drug Approval

To get a drug approved by the FDA to be administered and sold the drug must make it through many phases. The phases are outlined below along with terminology that is necessary for the understanding of the process.

<table>
<thead>
<tr>
<th>Toxicology</th>
<th>Determinants for toxic levels are compared with effective levels on two different animal species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>Clinical trials on normal humans without the condition being tested who are administered the drug to see if it is safe. Lower number of humans ~30</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Clinical trials on humans with the tested condition who are administered the drug. Middle number of participants~250</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Clinical trials similar to Phase 2 but with a large number of participants~1000</td>
</tr>
<tr>
<td>Phase 4</td>
<td>Drug has been approved and this is the marketing and distribution of drug and techniques of administration</td>
</tr>
</tbody>
</table>

Table 1: Terminology of steps of approval from FDA

The number of patients that are estimated above will depend on the condition and the outcome measures. The more patients that one has, the more power one will have on showing that their drug is significant and effective. The numbers vary off the condition and how conclusive the data has been in Phase 1 and Phase 2 trials.

Toxicology is in animals where one establishes what was the dose given, what was the formulation that the drug was made in, and how it was applied. All of these three aspects get rolled into a toxicology program. For example, it would give the background that they know at this dose and using this form of administration that their drug is effective. Now, they would amp the dose exponentially high and create a toxic effect. From this, one creates a ratio of the concentration that was effective to the concentration that the drug is toxic. This gap is ideally quite large for terms of treatment of the drug. This ratio establishes what the overdose level of this drug is and can be extrapolated to humans. What is toxic to the body?

The toxicology studies by rule have to be done in two separate species. For Prevacus’s case, rats being at the bottom of the evolution of the totem pole and humans at the top; they tried to find another species that is in between that evolution scale that could also be tested. One wants to see that in rats at this level it is toxic along with what is toxic for another species. In their case, they moved up to monkeys which are close to humans biologically. From this data, one would know that it takes this much of the drug
to make it toxic for rats and another level for it to be toxic to monkeys. With this data one can look at the evolutionary totem pole and see that from a rat to a monkey the toxicology levels change by this factor. From this, one can make a prediction for monkeys to human what level would be toxic, and that is the standard for establishing that ratio. One has thus established the ratio of toxicity to efficacy. Now they can go to Phase 1 clinical trials with a concentration that they feel can be effective and has no chance of being toxic. This gives one the best chance in Phase 1 that the drug at an efficacious level is safe in a human population and at that point one could move into Phase 2 on an effected population and see if it works.

In studying brain injury in Prevacus’s case, Phase 1 design can go a couple of different ways. The standard Phase 1 design is in normal humans, that haven’t had any kind of problem, in this case being a concussion. Phase 1 represents a safety study in usually a small cohort; in theirs, it is of 28 patients that are all human subjects. One goes through a SAD and a MAD meaning a single ascending dose and a multiple ascending dose respectively. What this entails is that a group of these folks will get a single dose and then in the MAD, the rest of the group will get multiple doses over a five day period. Then, one would establish that at this level with multiple doses or at this level with a single dose everything is safe. One will attempt to figure out what some of the side effects might be in their safety study. Nevertheless, one can do a Phase 1 with concussion patients. For instance, one can do a Phase 1A with normal humans, and a Phase 1B where one would actually incorporate concussed patients and strictly look at the safety. From this, one would want to get an idea that it’s safe after a concussion and not just safe with a normal human being.

Phase 2 is where one starts to look at the normal efficacy of the drug. There can be a Phase 2A where there would be an extension of the safety study and a Phase 2B, where they would look more into a concussed population. What is the key of these? The key is to be able to show first of all that it is safe and also be able to show that in Phase 2, the drug appears to be working. Keep in mind that Phase 2 is not a large number of patients. There is not near the number of patients that will be enrolled in Phase 3. In other words, Phase 2 is sort of a glimpse into the efficacy of the drug. In their case, there are a total of five different groups; 50 in each with a total of 250 different patients that will be enrolled into the Phase 2 trial. Groups include; brain injury with placebo, brain injury with two separate concentrations of Prevasol and brain injury given Prevasol for either 10 or 30 days.

This is where the rubber meets the road, with regards of trying to get the drug developed and passed by the FDA. It really begins in Phase 2. Usually everything’s pretty safe in Phase 1, and then Phase 2 is set up. This is where one wants to make sure they pick the right outcome measures to show that the drug is working. In other words, if the drug was to not improve memory, but reduce headaches and they don’t measure the outcome of headaches, they’ve missed the opportunity and lost everything. One cannot have 50 outcome measures because all the data would get diluted out and there would
be too much for the staff to handle and evaluate in Phase 2, let alone in a Phase 3 trial when the patient number is substantially increased. What actually happens is that one picks the right outcome measures and show that it works. If one picks the wrong outcome measures and it looks like the drug doesn’t work, the company is done right? On the other hand, they can go through another Phase 2 and pick the right outcomes to measure. In this case, one would not be out of the game but what it does mean is that one would have to re-spend the money to redo everything and often, these biotech start-ups cannot handle that blow.

If one outcome doesn’t show up and the other outcome does, it can be okay. This is based off the fact that the drug has been shown that it is effective enough and important enough of a measurable. For example, one has shown significant improvement in memory and learning but the drug doesn’t do anything to headaches. This would still be a good drug for concussion. What one would want to do in their outcome measures and what the FDA will push one to do is to prioritize their outcome measures. In order to prioritize their outcome measures, one will be a primary one and another will be a secondary, along with some tertiary measures. In their case, they look at the animal’s data and their most powerful effects of the drug are really on memory and learning. Thus, through a primary outcome measure they would set it up for with FDA to do a memory and learning test in humans and see if the drug improves the outcome. They know that with their drug they have a little bit of vasodilatory effect which should make sense to reduce vasospasms. If the headaches associated with concussion are related to vasospasms in the brain after a head injury, it would make sense that maybe the drug would reduce headaches, but that’s not going to be their primary measure. This will be a secondary or tertiary measure as it is more of a leap based on their preclinical data.

As for things such as imaging, if there was a severe brain injury with swelling, a CT scan and MRI will be able to show that. If there was a milder injury, the CT scan doesn’t pick up on it and an MRI can pick up on something if the proper software is used. Currently, there is only one form of diffusion tension imaging, which works for about 70% of the cases. In other words, what one may have is a washout effect where on 70% of the people it works and on the others, it does not. This may keep any significance from being seen if imaging is used as an outcome measure for concussion. When working with the FDA, imaging is really not what they focus on as a primary outcome measure. This is due to the reason that imaging does not relay or tell one the behavior of an individual or if the drug is making an individual function better. Given the state of imaging in a mild traumatic brain injury not being consistent today, it certainly would not fall as a primary outcome measure. It would be more of a secondary or tertiary measure.

One wants to pick the right outcome measures, but they also need to be prioritized based off the animal data that one has. Sometimes, animals don’t translate directly to humans and they may have been better off having headaches as the primary
measure. Yet, they would want to have enough secondary measures allowable by the FDA, to where if they did see a trend or significance that these could be valuable in getting the drug pushed through.

Phase 3 is where over 95% of drugs fail. With the cost of one drug being brought to market being an average of $17 billion this is highly stressful. The developing group may adjust something based off what they saw in Phase 2, but for the most part, it’s going to be similar to Phase 2, certainly if Phase 2 was showing great results.

In Phase 3, all the sites for testing get lined up and there is a contract research organization that oversees all the sites. One will go into this multicenter trial platform in order to get enough recruitment in a given amount of time. Due to the multiple sites, there are many hands in the cookie jar, which in turn creates more inconsistencies that can show up. To lower this problem, one must really have a tight control over the testing and feel immensely confident within their staff. At each site, it needs to be ensured that they are doing the exact same thing with the exact same measures in the same process. This is not always easy. If one gets 150 sites, they will never get that consistency. Rooting from this, one wants to minimize the sites they use for testing but not to a point where it makes the trial take too long to get enough patients for the trials to finish in a reasonable time frame. If one is looking at 800 patients, one would really want to go to six to eight different sites and at each site enroll anywhere from 100 to 150 patients. With this, one needs to be able to tightly control the staff and make sure that there are consistencies across the board.

For example, when Jake was with Emory, Phase 2 was all done at Grady Memorial Hospital, but for Phase 3, they recruited 31 other hospitals to do it quicker. What the Emory group ended up doing was having BHR Pharma create a partnership with Emory. The reason they partnered on that was to have another group be able to recruit hospitals internationally and BHR Pharma had originally started in Germany but had a presence here in America. This was going to allow them in combination to recruit many more patients. This was needed because there is not many moderate to severe brain injuries. There may be 8 to 12 severe brain injuries a year at local hospital so one must create a large multi-center clinical trial because one is only getting that many patients at each site to speed up the process. This still took approximately four years and BHR Pharma (SyNAPSE trial) signed up over 150 hospitals internationally while Emory University (ProTECT trial) had 31. This was over 180 hospitals across the world to have enough data to show to the FDA the efficacy of the drug. However, there are slight differences between the Emory and BHR Pharma trials and therefore both have had to be independently evaluated by the FDA for efficacy and safety.

The most important aspect of all these phases is the control of administration and outcomes. The big deal is that for whatever condition the drug is used for, the control of timing when the drug will be given needs to be addressed. Since the focus is on concussion, I’ll explain exactly where the pitfalls can occur. If in Phase 2 or 3 when
concussion patients are being given the drug, timing of the accident is crucial. The effect that Prevasol has on the patient if the concussion occurred 10 hours ago versus 30 minutes ago will be drastically different and affect the data of the drug’s effect on memory, balance, etc. Obviously from the studies on animals, administering the drug closer to the time of concussion has better effects on treatment than later on. Nonetheless, the time slot of patients and other characteristics like weight, severity of hit, and possibility of previous concussion are all critical to control to have conclusive data on the drug’s efficacy.

It’s been mentioned numerous times that so many drugs fail. This is the exact area that most fail. The control of the aspects mentioned in the previous paragraph is difficult to manage at one hospital let alone 8-12 that may be needed for the Phase 3 clinical trials. This will be the deciding factor if a company can make it or not. The drug will work; that’s the easy part. Showing that it will consistently work is the dilemma that needs to be solved for approval from the FDA.

IX. Barriers and Exceptions within the FDA

Navigating the approval barriers and taking advantage of exceptions are monumental to the success of the drug. As given before, below is a table to help with terminology and understanding of what will be explained.

<table>
<thead>
<tr>
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Table 2: FDA terms and processes

What needs to be done first before one can even initiate a clinical trial is a preclinical proof of concept study. This is when one creates a drug and creates a study set up to show that in an animal model it works for this particular condition. The best way to do this is to set up a study that has two things: a set of molecular data and a set
of behavioral data. One wants these to show that this drug works at the cellular level and that it also works at the phenotypic level such as it changes the behavior or an attribute that one can macroscopically see (the patient doesn’t have headaches anymore, they can memorize things, they don’t die, etc.) Once the proof of concept studies are done, and they feel good about the drug, one wants to patent all of this to protect the mechanisms and outcomes around this drug. For instance, it is made this way, it’s processed this way, the structure, the mechanisms of how the drug works biologically, and the behavioral effects the drug gives, one can all patent. The goal is to build a patent fence per say that surrounds all these different aspects of the drug. From the way it looks to how works.

The pre-IND meeting can reduce time to market by multiple ways. It can identify and avoid unnecessary studies, minimize potential for clinical hold, allow early interactions/negotiations with the FDA, etc. This meeting is used to prevent clinical hold issues from arising. A pre-IND meeting can also provide sponsors information that will assist them in preparing to submit complete investigational new drug applications.

The special population/military exception may not actually be deemed an exception through the FDA. The FDA sees that there is a need within a specific population and can be sold to this population to be used after Phase 2. This does not allow for a faster approval process but does allow for sales and thus revenue from the drug before it is ever approved. Prevacus will attempt to do this.

An NDA is the vehicle that companies formally propose that the FDA approves a new pharmaceutical for sale and marketing in the U.S. This is generally done during Phase 3. Its goals are to provide enough information to permit FDA reviewer to reach the following key decisions. Is the drug safe and effective in its proposed uses and do the benefits of the drug outweigh the risks. Next, the drug’s proposed labeling or package insert is appropriate, and what it should contain. Lastly, are the methods used for manufacturing of the drug and the controls used to maintain the drug’s quality are adequate to preserve the drug’s identity, strength, quality, and purity. Essentially, the NDA is supposed to tell the drug’s whole story, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies, how the drug behaves in the body, and how it is manufactured, processed and packaged.

A fast track designation is an alternative to the NDA that helps facilitate the development and expedite review of drugs and biologics intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. This program essentially makes the drug pre-approved so once it passes Phase 3; it can be sold without having a waiting period. Fast track adds to existing programs, such as accelerated approval, the possibility of a "rolling review" for an application. An important feature of fast track is that it emphasizes the critical nature of close early communication between the FDA and sponsor to improve the efficiency of
product development. This accelerated development path can create more value for the drug because it will allow more patent life for sales. Prevacus will attempt this.

A new chemical entity (NCE) is a drug that contains no active moiety that has been approved by the FDA in any other application submitted. An active moiety is a molecule or ion responsible for the physiological or pharmacological action of the drug substance. If a drug can get this designation it can give a drug five more years of exclusivity creating a longer life of the drug and thus creating more revenue.

Orphan disorders are essentially what is explained above in Table 2 and are present for only rare diseases such as Huntington and cystic fibrosis. This is rather appealing if one has a drug that has an orphan designation because the exclusivity extension adds on to the patent years of the drug being sold for a longer period.

For Prevacus, all of these are important. They are not an orphan disorder but will take advantage of multiple aspects explained in Table 2 with the special population being one of them. Albeit, for Prevacus, the ultimate goal is to have FDA approval and when Phase 3 is over the accelerated version will have allowed them to already have market approval by the end of Phase 3 instead of having to wait that year for the FDA to sign off and clear everything through. At that point, Phase 3 would go right into Phase 4 which is marketing; putting the drug out there for distribution from hospitals, clinics, sidelines, and military operations. An accelerated form of this could significantly reduce the amount of time in which this drug is available for patient use.

X. Drug Life: Reducing Costs and Increasing Profit

Patents pertaining to drugs only have a life for 20 years starting the day the patent is filed. Each addition patent filed will have 20 years from its date so to continue with strong revenue research and innovation around the drug is crucial to keep a patent fence around it. After 20 years, the rules for generics occur where any company can access that patent and use it to make a drug. Patent rules are all crucially important and ever changing in the biotech world. Prevacus has 12 patents/patent applications so far.

As toxicology was discussed early, one technically doesn’t have to show the toxicology data to the FDA. Eventually one will, but for Phase 1, one does not have to if they are doing their trials in another country. In Prevacus’s case, they are set up to do it in Australia. It’s fully approved, everything’s safe and already set up. It is the same test that would occur in the United States and there is a 46% rebate on a company’s costs. This method also allows the start-up company to get safety data before the company actually starts Phase 2 for approval from the FDA. In this case, the FDA has already seen that they have safety data and that strengthens their case to get approval. Conversely, if they were doing Phase 1 in the states, one would have to have a pre-IND meeting with the FDA to receive approval to start Phase 1. Due to this, many of the start-ups do it out of the country to make it quicker and it is cheaper.
To receive the rebate, the company has to create an LLC which one would put money into within Australia with enough money to fund the entire trial at the same cost it would be here in the states. Then, since Australia is recruiting business for companies to come there, they give a 46% rebate on the costs charged. This is presumably to help build the economy over there and they want this business so they will basically give it to one at half the price. They know the FDA approves the clinical data that comes out of there, so why wouldn't companies do it? For Prevacus, originally what they thought was possible was that they could get away with just doing one species of toxicology in Australia which would have reduced cost and time to complete Phase 1. It turns out that this is not the case, and they still have to do rat and monkey species. For them, the reason for doing it over there was that they are just as competent as the states and it is cheaper for the shareholder along with speeding up the approval process by a margin.

After Phase 2 has occurred and received the right outcome measures the company will obviously move into Phase 3. What does that mean to the investors and to the drug development? Phase 3 is usually a multicenter trial and it is this simply because it is set up to enroll enough patients in a given time frame to try to streamline the timeline for the development of this drug. If one just chose one hospital it may take them 20 years, but if 20 sites are chosen it may only take one year to complete.

XI. Financing and Milestones

From an investor standpoint, when an investor takes part in a biotech start-up, at the beginning, they are taking on an enormous level of risk. All the start-up has done is animal studies and they are likely just getting through toxicology to show that it isn’t unsafe in animals. Then one has to enter into Phase 1 showing safety, and all of a sudden investors have hung in there long enough that the company is developing and growing enough to get through Phase 2 showing positive outcomes and being able to enter Phase 3. That’s when the company can sell; after Phase 2. No big pharmaceutical company is going to want to take the risk on any drug in the preclinical toxicology or Phase 1 clinical trial; there is just way too much risk. One has not even shown proof of concept in humans that this drug can even have an effect. Once one has gotten through Phase 2 and shown in their case with 250 patients that it is efficacious, one is ready to enter Phase 3. Then, the company is now an entity that can be seen as valuable to a big pharmaceutical company.

Years and years ago, these big pharmaceutical companies used to have their own preclinical development. They used to outline a design and push their own Phase 1 clinical trials; their own toxicology studies. A company like Prevacus would have been competitors with them. Now, Prevacus is basically an arm that takes a risk for big pharmaceutical companies in regards of drug development. What they end up being is in a position to sell after Phase 2. Pharmaceutical companies would pick their drug up and they would carry it through Phase 3.
What does this mean for an investor? Pharmaceutical companies will generally not come out and buy the company and pay for the license of the drug after Phase 2 in a full amount to its value. Let’s say they view this as a drug because there are so many concussions that it could bring in $3-$4 billion in revenue a year if it makes it through Phase 3 and then can be marketed. They know they can bring in $3-$4 billion in revenue a year off this drug, but they know they also are still taking the risk of making it through Phase 3. They are not home free.

The pharmaceutical company is not going to give one $3 to $4 billion but let’s say they decide to give them $800 million. They will buy the license of the drug and all the patents and everything like that. They will not give $800 million upfront. They may give half of this, say $400 million upfront. Investors are going to get paid out of the $400 million and they will get the rest of the payment if the drug makes it through Phase 3. If it makes it through Phase 3, there will be a back payment or in other words called a milestone payment. The milestone would success in Phase 3, and that payment would go to the investors at if the milestone was successful.

The investors are still not exactly home free depending on where they are in a stock format. There is something called common stock and something called preferred stock. Preferred stock has different series: series A, Series B, series C, etc., with more series due to a company going through development. What Prevacus did, was originally take Jake, the founder of the company, and give him common stock, and with common stock there are higher voting rights than preferred stock. The next round, the first round of equity was the “friends and family” round. Those were originally promissory notes that got converted to preferred “series A” stock. Now if it ended there, they got paid for equity and the company got through Phase 2 trials and is bought, the preferred stock investors are going to get paid before the other (common stock) investors. In this scenario, Jake would be the last person to get paid in a liquidation event. With that said, the decision making power that Jake has in terms of voting power to a preferred stockholder is much higher. For example, if someone owns 10% that is of common stock, they will get close to 15% voting power. This is a third more and thus quite significant.

They then go into Phase 3. The company has been bought and Phase 3 is successful, they will file what is called an NDA, or a new drug application. The FDA approves that NDA in six months to a year down the line and then one can classify themselves as a company with a drug that they can market and sell. It’s likely that a big pharmaceutical company can recognize this specific epidemic for the drug and then they can enter Phase 4, which is a marketing phase of the drug. They market the drug, create a sales force to get the drug out to doctors and hospitals, and market development with post market reminders when pharmaceutical reps come on board. From here it seems to be over, to the point to what patents are hooked to the license. Let’s say big pharma has bought the company and owns the license, and when one sells it after Phase 2, they also forwent any patent royalty. What the big pharma company receives in that
situation are the patent royalties. If the company had not sold the patent royalties, the situation is completely different.

If the company did not sell all their patent royalties, let’s say a certain percent, Prevacus would continue to get paid a certain percentage from the sales throughout the life of the patent. For numbers sake, let’s say Prevacus has 1% of patent royalty, and big pharma was selling $3 to $4 billion a year for the drug. Prevacus would get 1% of that $3-$4 billion for how long the life of the patent is, being a life of 20 years from the time that the patent is originally filed.

However, from this original time, it may be 10 years before there’s any revenue, so in that case one is only going to get 10 years worth of patent royalties before that specific patent expires. What happens after the patent is gone? When it goes away, the drug method is accessible to anyone so generics enter the market and sometimes it becomes over-the-counter. Nonetheless, these companies that own these drugs for whatever given amount of time was needed to develop the drug minus the years they had the patent, is how many years they have sole rights to sell it.

Financially, if one were to accept royalties in the buying of one’s drug, they may get paid less. From this situation, one may get paid in a smaller lump sum but it can be a beneficial gamble for the owners if the drug works because in the end, they would earn more from that specific royalty paying over the years that the drug is sold. Some founders of the company, as in Jake’s case, view it in a different mindset. They see it that they would go ahead and give away the royalties so the investors could get a higher amount for what they had invested in as a gift to the investors. Yet, no one knows what they’ll be thinking at the time.

Now there is a vote. The drug company is ready to sell and they can negotiate a patent royalty at a certain level. Let’s say there are 50 investors, and 26 of them want to get paid now and 24 of them want to get paid less but maintain a royalty position. In this case, it comes down to who’s got the most voting shares. For Prevacus and Jake, this goes back to the value of Jake having common stock, which the common stock holders will have the most influence on this matter due to voting power. In Jake’s case, he has a strong voting power and since he knows everything about the drug if there was a decision on the best route of action, some investors would probably come on his side for voting.

From Jake’s stand point, without a patent they would receive based off our previous purchase example, $400 million up front and $400 million on the backside. However, if a royalty is included, they may only receive $200 million up front and $600 million on the backside. If that royalty is included and the drug fails in Phase 3, the company just lost $200 million because of the gamble for the royalty stake that adjusted what money would be given up front. If one was an investor and Jake gives up the patent royalties, they receive $400 million but if he keeps them, they only get $200 million. The investors are pretty much thinking that Jake’s got to take a risk for it to get
to Phase 3 and they will never get any patent royalties. What if Phase 3 fails, then they just threw away $200 million, but if it is successful, they will get all the money originally and they have the patent royalties for the life of the drug.

This decision would likely be based off how positive the results of Phase 2 data is and be based off the team that would buy the drug and how great they are at development in bringing these drugs through FDA approval. There could be a contingency case as well to keep Jake and his scientific team on in some sort of oversight position to assist the pharmaceutical company in final development. The hope is that someone that buys it is extraordinary at developing drugs, which would allow Prevacus to be able to risk a little bit more in making royalties a part of the deal.

One will also have many other people involved voicing their opinion on the royalty or lump sum matter. Basically, it’s an educated statistics game. If there is a 51% chance that this drug will work, would one risk the little chance of value of more income for $200 million? Probably not. What if it was 75% chance of working? All day, every day that gamble is made. What if it was 60%? Now that probably depends on how one is feeling that day. Ultimately, at the end of the day, it’s going to be a choice from many people to choose what should be done, which is quite a good thing because they are evaluating it for the best opportunity possible.

XII. Taxol: A Settlement for Thought

Another story of royalties is the Taxol story at Florida State University. Robert Holton came up with the semisynthesis pathway that was 80% effective and caught Bristol-Meyers Squibb (BMS) by storm. It was a quicker more effective way that could not be beaten. It was a faster, more efficient way that a company could use to be more profitable. While the molecule he could not patent, he did patent the process. This process included the mechanisms, dosage, and steps to achieve this drug at such an efficient rate. Holton’s lab and FSU had patented that process in 1992 and BMS had it in the market by January 1993, giving them approximately 20 years of patent usage rights (Stephenson, 2002). FSU’s contract was for a royalty rate of 4.2% of BMS’s worldwide Taxol sales (U.S. Government, 2003).

With sales starting in 1994, FSU had received over $200 million in royalties with Holton receiving 40% of these from an inventor rights bylaw through the university. For Jake’s case with FSU, he gets 40% of whatever patents are made, so if there was a 10% deal, FSU would get 6% and Jake would get 4%, giving Jake and FSU revenue generated by their patent over the life of the patent no matter what company is selling it. If the patents and royalties were set up under Prevacus Inc. and not FSU, the royalty income comes back to the investors. There percentage of royalty income will be correlative to what percentage of the company they own. So for numbers, let’s say the company receives a patent royalty of 5%, and Jake owns 20% of the company, he will get 1% of the overall patent royalties, being 20% of the 5% that they got. The stockholders would get the rest based off their certain percentages that they owned.
XIII. Current Time and the Future

Currently, Prevacus is in toxicology testing with rats and monkeys to determine toxic levels and the gap between those compared to the effective dose. They have Phase 1 trials already set up in Australia, at Cmax and Nucleus, Inc. with significant cost savings. Once toxicology is finished, Phase 1 will begin. Yet, it is somewhat of a race so the company can have a longer patent life for the drug, when the drug makes it to market. The future looks bright, but there will be problems that arise. Prevacus’s success will rest solely on how these problems are addressed. I have full faith in them and I know the help that there drug can do for mankind. Despite the failure rate in pharmaceutical development, with the drug they have and the leadership team, this will be a new drug in the coming years and the first of its kind for mild TBI.

XIV. Acknowledgments

I would like to give thanks to Jake, Mike, and the whole Prevacus family for the knowledge they’ve shared with me and the love they’ve shown. Additionally, I would like to thank Ron for being the absolute best thesis director and always being there for everything including structure, organization, and mentorship, etc. I would also like to thank Doug for giving me guidance, fellow contacts in the subject matter, and tough love when things needed to be fixed. I love you guys and you all are the best!
Reference List


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