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GB Sciences – using Minimum Essential Mixtures (MEM) to Harness the Therapeutic Potential of Plant-Inspired Medicines as Prescription Drugs

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CEOCFO: ***Dr. Small-Howard, the first thing I see on the GB Sciences website is "The Future of Healing." Would you tell us the overall idea behind the company?***

Dr. Small-Howard: At GB Sciences, our goal is to harness the therapeutic potential of plant-inspired medicines as prescription drugs. We have approached our central mission using both our proprietary AI-enabled drug discovery platform, as well as bioactivity screening platforms using cell and animal models of disease. Initially, we were focused on discovering simple mixtures of compounds from within the cannabis plant for which we were able to demonstrate therapeutic effectiveness and molecular synergies between the active ingredients in these minimum essential mixtures (MEM). We have now expanded our reach, and we are looking for MEM from other plants as novel therapeutic interventions. We have accomplished this new phase of our development by building out a novel database that is globally rooted in traditional medicines. This powerful, structured database is at the heart of our proprietary, AI-enabled drug discovery platform, PhAROS™, which stands for Phytomedical Analytics Research Optimization at Scale.

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We think that our approach is quite novel in that there have been companies striving to bring pharmaceutical products to market by looking within traditional medicines, but they are not looking to harness the potential within traditional medicine in a holistic way informed by the epistemology of these medicines, which relies on combinations of ingredients working together. In contrast, the western pharmaceutical approach to utilizing plant-inspired medicines is to identify a single high affinity ligand for a single drug target from within a complex mixture of plant-based ingredients. However, the 'single drug target' approach is not working out very well for patients. Currently greater than 50% of all Americans are on four drugs, one drug to address their chief complaint and three drugs for treating the side-effects of their initial drug. We now know that most human diseases are complicated, and they do not reduce simply or neatly to a single receptor-based drug target. The 'single drug target' approach may be outdated, and we, and others, are looking towards a synergistic network pharmacology approach to the development of new therapies.

We believe that by augmenting drug discovery with modern *in silico* processes, we should be able to create a more complex *in silico* model of human physiology, and, ultimately, utilize the 'side-effect profiles' or off-target effects, intelligently integrated as a part of what a drug can do therapeutically. We are essentially trying to integrate traditional medicines and the power of digital processing to create a different kind of drug discovery process that predicts the effects of multiple ingredients working together in a digital system modeling human physiology. This new AI-enabled drug discovery model would potentially improve our ability to address complex disorders, and it allows for preplanning of the side-effect profiles, so that they are therapeutically useful as opposed to harmful.

CEOCFO: *Why has this not been thought of before?*

Dr. Small-Howard: In the past, we did not have the digital processing power required to rethink the fundamentals of drug discovery and development. Also, the single drug target approach is deeply entrenched both within drug developing companies and the regulatory agencies that evaluate new drugs. Because the single drug target system has worked in the past, few developers have been in a position to challenge the status quo. Single component drugs are simply easier when you are setting up the experiments and for understanding the results. If you have one thing to track, it is easier to explain what is going on. I think we are now firmly in the digital era, but there has been a lag in the adoption of AI-enabled processes in drug discovery relative to the digital transformation of other industries. Before computers you had to set up a simple system so that you could easily interpret the results, but we can now analyze and understand the patterns in complex data sets. Human biology is complex and disease processes are even more complex. Before we had modern computing power, if we set up experiments with the complexity that we are using now, we would not have been able to understand the results. Currently, I think we have the perfect storm of digital power and access to the sharing of ideas within traditional medicine. We did a lot of work with ethnobotanists that study natural medicines, which helped us not only have access to some of the ideas within traditional medicines, but also to improve upon traditional medicine in a way that can lead to novel, scalable therapies.

Approximately 65% of the world uses traditional medicines to treat disease, some in conjunction with Western medicines, but others rely on traditional medicines as their primary medicines. I think that in the US and other parts of the western world, we do not realize the true potential of traditional medicines or that they are currently helping people globally. Traditional medicine, by definition, is very localized and based on what grows in your area; whereas the kind of system that we are trying to create would take some of the principles of traditional medicine but expand upon it so that you could globalize these treatments.

CEOCFO: ***Will the US FDA come into this at some point?***
Dr. Small-Howard: Oh, absolutely. We believe that we have a strategy for that.

CEOCFO: ***How are you preparing and why do you think the US FDA is ready to look at this in a fair way?***
Dr. Small-Howard: Our approach should help with translating plant-inspired medicines to the prescription based pharmaceutical market. Our approach to modernizing traditional medicines begins by identifying the ingredients in the natural product most responsible for its therapeutic effects, creating something that we call a 'minimum essential mixture' or MEM, which should be easier for the US FDA to evaluate as an Active Pharmaceutical Ingredient using their standard processes than the whole plant extracts in the original traditional medicine. Using a combination of AI-enabled processes and screening in cell and animal models, we sequentially reduce the complexity of a traditional medicine derived from whole plant extracts that originally contained hundreds of active ingredients down to between three and five active ingredients in the MEM. Three to five active ingredients per MEM may sound overwhelming if you are a person that is used to looking at single-ingredient drugs, but it is a dramatic reduction in the complexity relative to what was in the original traditional medicine product.

Not only are we reducing the number of ingredients from the original traditional medicines in our novel MEM therapies, but we are also using intelligent design to define the interactions of these active ingredients. Simply put, we are looking for molecular synergies within the active ingredients in our MEM. We have demonstrated that the efficacy of each minimum essential mixture is greater than the sum of the effects of the individual active ingredients. It is by utilizing this definition of synergy that we have been able to patent our minimal essential mixtures. Because of the molecular synergies, we can demonstrate that there is increased effectiveness, which is not only a great way to get over the obviousness claim at the USPTO, but it also means you are making more effective medicines, so it is a win/win.

In the manufacturing of our MEM, we are also substituting synthetic homologues into the mixtures instead of the plant-based ingredients, as yet another strategy for making our MEM more US FDA friendly. These synthetic homologues are identical copies of the original plant-based ingredients, but they can be made at scale in giant vats in a warehouse under cGMP conditions. This allows us to formulate our MEM at scale without the need to grow any plants. Plus, the US FDA will have all of the data on the manufacturing of the individual ingredients for their

assurance that these API are safely and consistently produced. Also, the strategy for the manufacturing of our formulations allows us to more easily file a standard New Drug Application (NDA), rather than having to file for approval under the Botanical Drug Development program. In the history of the decades old Botanical Drug Development program, only three or four products have ever been approved. We like our odds better at complying with the standard Pharmaceutical Drug NDA pathway.

In summary, we are trying to harness the therapeutic power of medicinal plants by reducing the formulation complexity down to Minimum Essential Mixtures (MEM), demonstrating the effectiveness of the molecules working together, and substituting synthetic copies of the plant-inspired active ingredients so that we can file a standard NDA.

Lastly, we are formulating our plant-inspired MEM using modern proprietary delivery techniques. For example, our lead program is a Parkinson's disease therapeutic, and we are utilizing an oral dissolving tablet format or ODT, which is an excellent delivery mode for these patients. Half of all Parkinson's patients have a hard time swallowing. The oral dissolving tablet is an excellent format to not only enhance the stability of the active compounds, but these ODT also dissolve easily on the tongue, so it is a perfect solution for patients having problems swallowing.

For our chronic pain formulations, we are working with the University of Seville in Spain to develop time-released oral nanoparticles of our novel MEM. If you talk to patients with chronic pain, they are very concerned about maintaining pain relief over time. Because the standard of care for pain relief is opiate-based drugs, drug 'tolerance' is a real problem. Tolerance means that the more you take the drug, the less effective it is therefore, you have to increase the dosage and frequency to maintain pain relief.

Not only are we striving to create non-opioid options for people with chronic pain, but we are also trying to put them in time-released oral nanoparticles to better maintain their pain relief over time. For example, in our proof-of-concept studies in rodents, a single dose of these oral time-released nanoparticles was able to relieve pain for eleven days, relative to less than 24 hours of relief from the same cannabinoid compound without the nanoparticle vehicle. In utilizing these powerful plant-inspired molecules augmented with modern delivery methods, we can better help patients by considering the kinetics of how the medicine gets into their bodies and how to keep that effect active over time. Taken together, we believe that our research and development strategy will help us predict and overcome any regulatory issues.

CEOCFO: ***How do you decide what to work on?***

Dr. Small-Howard: Although our drug discovery process is flexible enough to work on therapies for almost anything humans need or want therapeutic help with now or in the future, we have had to be very selective as a company to preserve our resources. We have five active therapeutic programs right now, and they were selected partly because we thought this was an area of great clinical need and partly based on the advantages of our products relative to the competitive landscape.

Additionally, the quality of the data that we used to demonstrate efficacy is a factor as we move projects forward in our pipeline. Like most companies, we have tried many different things. Sometimes they worked and sometimes they did not. All these factors have shaped the selection of the products in our current biopharmaceutical pipeline.

CEOCFO: ***Do you have products available now? What does the business side look like?***
Dr. Small-Howard: We are a company that has pivoted. When I originally joined GB Sciences, we were a cannabis producing company. I joined because I had done my graduate work on the potential to use cannabis ingredients to modulate the immune system, and I knew that there was something there to be discovered within the plant therapeutically, but it was hard to work on in academia. The way that cannabis is scheduled made those experiments difficult to complete and there was very little federal grant funding for those types of projects back then. When the state-regulated programs for medical cannabis were becoming a reality, I thought to myself that there was a real opportunity to make medical products informed by real science by joining forces with a cannabis producing company.

Research funding and cannabis plant materials were the two things that were the hardest to come by when I was doing academic research on cannabis. At that time, there was only one place in the country allowed to grow cannabis for research and there was a very complicated series of written permissions required to have it sent for your research. It was equally hard to get funding, especially if you were proposing to demonstrate any therapeutic benefits from cannabis. Back in the day when I did my graduate work, the only place you could get money to do cannabis work was through a part of the NIH called NIDA, which is the National Institute for Drugs of Abuse. Because NIDA's main mission was to research the harmful effects of drugs of abuse, if you were applying for their grant program you had to be looking for data supporting the hypothesis that cannabis was harmful. It was difficult for them to give grants for studying the therapeutic potential of the plant at the time. NIDA has changed their granting policies since then, but this was the way it was when I was starting out in the early 2000s.

When I joined the company, our goal was to produce cannabis and cannabis-based products using scientific means to unlock its therapeutic potential for patients by enhancing the safety and consistency of our formulations and by using data to support its efficacy. We have now pivoted. We sold all our plant-touching assets, and we have doubled-down on our biopharma program. Right now, we are a publicly traded company that is investor supported. We have apparently found like-minded folks that believe in the power of plants, and they have continued to support our novel plant-inspired research and development pipeline.

CEOCFO: ***What is your plan for the next six months to a year?***
Dr. Small-Howard: We are focused on getting our lead program into the clinic, which is a novel therapeutic for Parkinson's disease. We are currently working on our IND-enabling studies, and our goal is to get our pre-IND package for our Parkinson's therapeutic submitted to the US

FDA by the end of next year. We also have a chronic pain program, an anti-inflammatory program, and a heart disease program in process with significant milestones being achieved. One new development program that I am very excited about is our kava-inspired anxiety program. This is our first non-cannabis inspired program, and we have now achieved the statistically significant reduction of anxiety in an animal model. That is exciting for us. Within the following year, we hope to file our pre-Investigational New Drug Application to kick off our first-in-human trial for our Parkinson's therapeutic, as well as to report significant progress in moving the rest of our programs forward in our biopharmaceutical pipeline.

CEOCFO: ***How do you deal with some of the frustration when you know you have ideas that could make a difference in peoples' lives and it is a long and arduous process to get them into use?***

Dr. Small-Howard: I simply accept that we are playing the long game. I have experience in the biopharmaceutical industry, and I have successfully taken products from ideation through commercialization. So even though it is a long process, it is a process that I understand and that I believe will ultimately serve patients better. For all its challenges, the biopharmaceutical process produces safe and effective products with nearly global access. I believe that taking the long road to get these validated medicines into the pharmacy is more beneficial for patients, than if we try to use a nutraceutical route, which I have done in the past, or if we had stayed in the medical cannabis space. While there are product shortcuts, I believe you can help the greatest number of people achieve superior therapeutic results using a process that is regulated to help enhance the safety and effectiveness of the products you are producing by taking the long road to the pharmacy.

CEOCFO: ***From the perspective of the investment and medical communities, with so many options for people to consider, why should GB Sciences standout?***

Dr. Small-Howard: When it comes to developing new drugs, a lot of the low-hanging fruit has been picked. What we find is that there are a lot of me-too therapeutics being developed based on the single drug-target model. We propose a radically new way to bring plant-inspired medicines to the pharmaceutical market, and we hope it will change the way that all drug development is done. If we can really lean-in to the strengths of AI-enabled drug discovery processes, we can start looking at human beings in a more holistic way. So instead of taking those four drugs that you take, you may have one compounded formulation that will help you. Right now, we are looking to treat groups of patients that are similar, but in the future, we are talking about real personalized medicine. None of this would be possible without using novel digital processes that are being improved upon as we speak.

A more pragmatic way to view the value that GB Sciences' offers is to look at the significant milestones we have coming up in our biopharmaceutical pipeline. We have come a long way, and we are getting closer to the clinic every day. Shareholders will enjoy an increased valuation during our transition from a pre-clinical to a clinical development company. Also, when we start getting positive clinical results, then watch out! The valuation of our drug development pipeline

will likely increase again, significantly. We look forward to what the future brings for GB Sciences, and we are ready to traverse the long road ahead to bring plant-inspired medicines to the pharmaceutical market.