Camargo/XenoTech Case History:

Utilizing the 505(b)(2) Pathway to Streamline and Accelerate a Drug Development Plan

Background

An international pharmaceutical company approached Camargo Pharmaceutical Services to help navigate the Food and Drug Administration (FDA) 505(b)(2) approval pathway for a promising drug under development designated for patients with cardiovascular disease. Product X is a prodrug that is converted in one metabolism-dependent step to produce the active metabolite of an approved drug. Camargo, a company with broad experience in drug development, specifically the 505(b)(2) pathway, needed to bring advanced analytical technologies and specific drug metabolism expertise into the client's proposed development program. Camargo chose an innovative way to achieve this by forming an alliance with XenoTech, LLC, a leading contract research organization in the drug metabolism field. Together, Camargo and XenoTech designed a complex initial development plan that generated critical data to establish a bridge between existing literature and data for the approved drug. This information was presented at a Pre-IND Consultative Meeting with the FDA to obtain agreement of the client's proposed streamlined development plan.

Objectives

- Establish the appropriate species to build a toxicological bridge to existing data for the approved drug.
- Evaluate the dose response and dose equivalency of X and the approved drug.
- Obtain the FDA's input regarding the appropriateness of a 505(b)(2) regulatory pathway for X.
- Gather advice from the FDA on the proposed drug development plan for X.

Challenges

When the approved drug was developed, there was little known about its metabolism. Therefore, establishing the equivalency and differences between X and the approved drug required that both drugs be subjected simultaneously to nonclinical testing in ways that permitted comparison. This essentially doubled the nonclinical workload.

Camargo turned to XenoTech to form a partnership, melding their capabilities into a working unit that could design and complete a long list of complicated studies in a shortened time frame. Camargo is considered by many to be the industry's leading 505(b)(2) expert and brought its unique research capabilities and knowledge of the FDA regulations and processes to the table. XenoTech's team has experience with complex metabolism studies for a wide variety of drug candidates, state-of-the-art technology and specific experience with the compound of interest. However, joining together two highly trained teams of scientists for a relatively short-term, high-pressure project required an exceptional level of communication and collaboration.

About Camargo Pharmaceutical Services

Camargo Pharmaceutical Services is full-service drug development partner specializing in the 505(b)(2) approval process. Camargo works with companies across 26 countries to expand portfolios and develop compounds with lower risk, reduced cost and faster speed to market in an increasingly competitive landscape. From before development even begins, Camargo verifies profit potential by developing a comprehensive program and timeline complete with important milestones and cost objectives. Camargo manages every facet of the plan throughout the development continuum, from feasibility assessments, formulation and testing the drug product, to conducting preclinical and clinical studies, to final submission. Connect with Camargo on LinkedIn, the President's blog (www.camargoblog.com) or visit **www.camargopharma.com** for more information.

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About XenoTech, LLC

XenoTech is a contract research organization with unparalleled experience and expertise in evaluating drug candidates as substrates, inhibitors and inducers of cytochrome P450 enzymes and other drug metabolizing enzymes and drug transporters. The company offers a variety of *in vitro* contract studies for drug candidate evaluation, as well as an extensive selection of products for drug metabolism research. XenoTech's product selection includes a wide range of high-quality standard reagents, from subcellular fractions and hepatocytes to transporter membranes, and the company can also prepare and deliver custom-designed products and services in response to client requests. For additional information, please refer to the company's website at **www.xenotechllc.com**.

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Approach

The client approached Camargo with the concept that X could be superior to the approved drug in several areas:

- Reduction of inter-individual variability and more consistent drug effect, including individuals who are considered poor metabolizers, compared to the approved drug.
- A faster onset of action than the approved drug.
- Minimization of drug-drug interactions when compared to the approved drug.
- Improved safety profile, especially when compared to newer drugs in the same class.

Assessing these areas required filing an Investigational New Drug (IND) application with the FDA to administer X to humans in a clinical trial. Camargo and XenoTech jointly developed the series of studies designed to provide the necessary data for a successful pre-IND meeting.

In vitro hepatocyte and intestinal microsomal metabolism studies helped establish the case for toxicology testing in a single animal — an accomplishment that in itself saved the client substantial development costs and time. Among the species tested, monkey hepatocyte profiles were the closest match to human hepatocyte profiles for both the approved drug and Product X incubations. The monkey intestinal microsome profile also most closely matched the human microsome profile. These data were further confirmed in a radiolabeled *in vivo* ADME study in cynomolgus monkeys.

CYP450 inhibition studies demonstrated that X directly inhibited CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5, and may also be a metabolism-dependent inhibitor of all except CYP2D6. P-glycoprotein drug-drug interaction testing indicated there was no active transport of X by MDR1 through MDCKII-MDR1 monolayers, and, in fact, that it is likely that X is a low affinity inhibitor of P-gp.

In addition, the client provided critical data from a study evaluating the pharmacodynamic effect of X in an animal model, which suggested the effectiveness of X compared to both the approved drug and newer drugs. Data from these studies as well as data from existing literature and data from the approved drug were prepared for presentation to the FDA in a formal pre-IND meeting.

Outcomes

Based on the preclinical results and the regulatory arguments presented to the FDA, discussions with the agency at the pre-IND meeting resulted in several promising key outcomes including the following:

- The FDA agreed with the streamlined development plan proposed by Camargo.
- An abbreviated nonclinical development program was found acceptable, including the use of only one species for definitive toxicology studies and no carcinogenicity studies assuming the standard genotoxicity panel was negative.
- The FDA requested only one additional *in vitro* metabolism study, which would allow reliance on the full reproductive and developmental toxicity studies performed with the approved drug.
- The FDA recognized that if Phase I studies demonstrate that X has the expected properties, fast track designation may be granted.

Conclusions

In most cases, gaining IND approval is a tremendously complicated process, taking years and costing well into millions of dollars. By combining the expertise of two unparalleled leaders in their respective fields, an in-depth nonclinical and clinical program was avoided, potentially leading to a substantial reduction in the time to market approval. The total cost savings combined with the significant marketing advantage as compared to other approved drugs in the same class has the potential to ultimately return generous profits to the client.

Succeeding in drug development these days requires more than just a promising compound. It requires the specialized knowledge that can only come from being on the front lines in the development of scores of different compounds.

XenoTech's hepatocyte and intestinal microsomal metabolism studies helped establish the case for toxicology testing in a single animal; Camargo made the argument for utilizing the 505(b)(2) regulatory path to streamline the drug development plan for Product X. The combined efforts of this duo allowed the client to rapidly complete a significant amount of complex preclinical testing and to produce a drug development plan that will result in substantial savings in time and money.