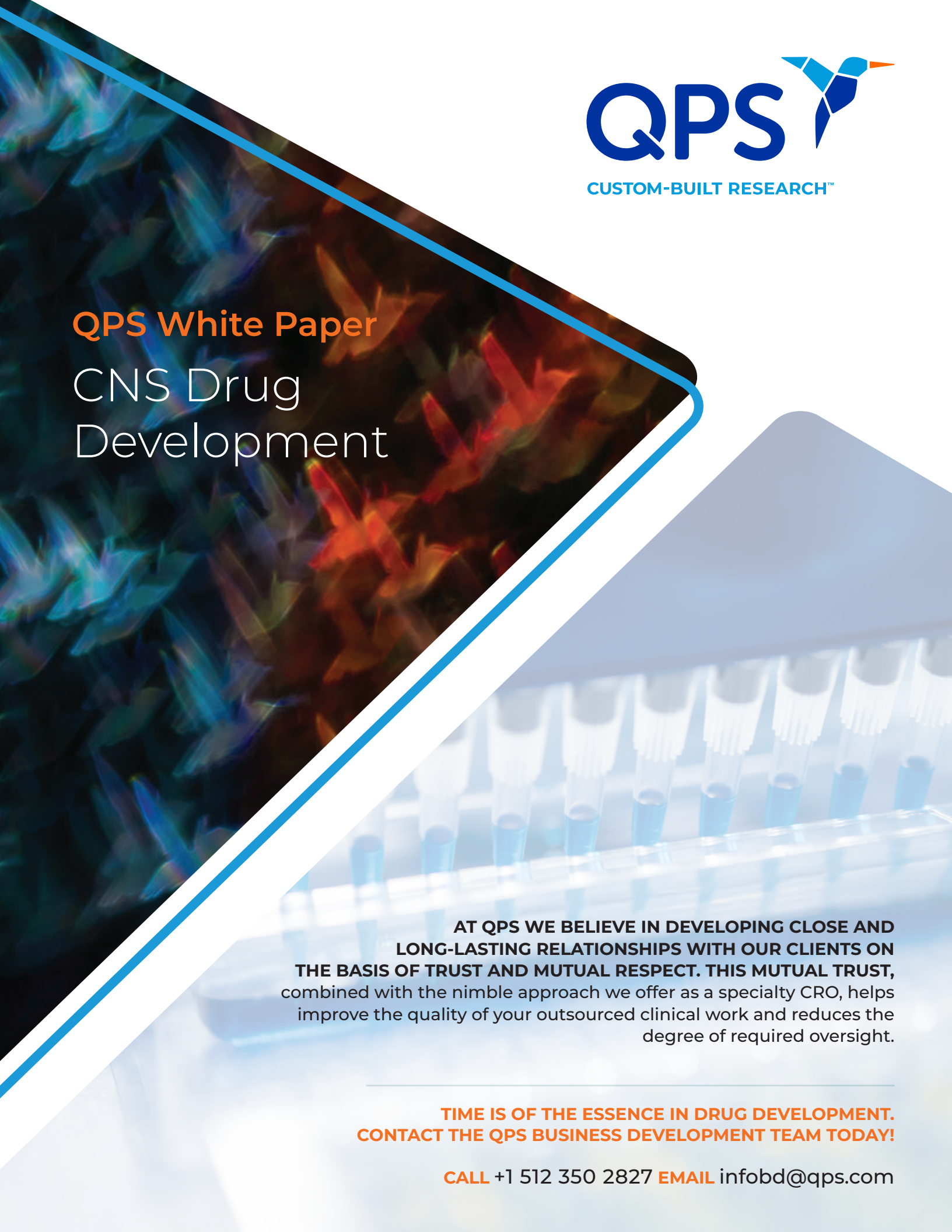
QPS

CUSTOM-BUILT RESEARCH™

QPS White Paper

CNS Drug Development



AT QPS WE BELIEVE IN DEVELOPING CLOSE AND LONG-LASTING RELATIONSHIPS WITH OUR CLIENTS ON THE BASIS OF TRUST AND MUTUAL RESPECT. THIS MUTUAL TRUST, combined with the nimble approach we offer as a specialty CRO, helps improve the quality of your outsourced clinical work and reduces the degree of required oversight.

TIME IS OF THE ESSENCE IN DRUG DEVELOPMENT. CONTACT THE QPS BUSINESS DEVELOPMENT TEAM TODAY!

CALL +1 512 350 2827 **EMAIL** infobd@qps.com

FLEXIBILITY. AGILITY. SPEED.

QPS CUSTOM-BUILT RESEARCH™

Introduction

QPS provides essential preclinical and clinical research services to help pharmaceutical and biotechnology companies around the globe accelerate the discovery and development of drugs to prevent, treat and cure brain diseases, with a special focus on age-related neurodegenerative disorders such as Alzheimer's and Parkinson's Disease.

Developing therapies for diseases of the central nervous system (CNS) presents special challenges directly related to the complexity of the human brain and its function of integrating our communications with the outside world. Animal models of human neurological and psychiatric disorders are scarce, because many of these human diseases do not naturally occur in animals, and their study necessitates either specific manipulation (induced models) or the production of genetically modified rodents (transgenic and KO models). Even with these models, it remains unclear, what behavioral domain really resembles higher brain function in humans, and how we can interpret animal data on cognition, emotion, social interaction or activities of daily living.

Furthermore, in contrast with other organs, the CNS is sequestered from the general circulation by the blood brain barrier (BBB), potentially preventing many compounds from reaching their intended target. Quantifying how much of and how long a compound resides in the CNS is difficult and indirect. Therefore, the assessment of target engagement calls for specific techniques and know-how. While animal models provide some information as to how well a given compound accesses the brain, this data cannot always be translated directly to humans. Insufficient knowledge of target-compound interaction may be a major cause of failure in drug development for CNS disorders.

QPS understands the specific challenges of translation from animal models to human clinical application. Our extensive experience in CNS affords us a clear view of its complexities and its current global clinical study environment. Our direct links with the international scientific community and close relationships with key opinion leaders worldwide, together with our dedicated experts, original strategies and operational transparency, are keys to the effective execution of CNS programs for our clients.

QPS' Preclinical Services

Neuropharmacology

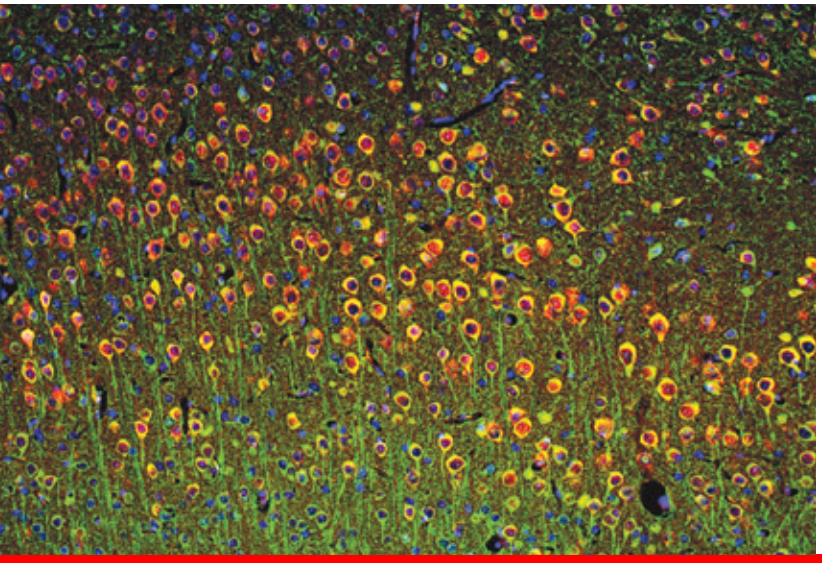
QPS provides a wide range of pharmacological research tools for CNS disorders. Not only do we offer *in vitro* techniques using cell-free systems for new drug efficacy investigations, but we also offer a wide range of tissue culture methods which allow medium to high through-put screening on neuronal cultures. This process is ideal for investigating the effects of new chemical entities on an already complex system. Depending upon the target indication and the proposed mode of action, we can select the most appropriate tissue culture system, whether it be primary cultures from transgenic rodent models or one of a wide range of commercially available neuronal cell lines. Furthermore, depending upon the research question, we can stably transfect these cell lines with any gene of interest that would enable high through-put screening or allow a more precise assessment of the test substances' properties.

Our experience with cell systems ensures a reliable selection of the most potent compounds, and at the same time, *in vitro* safety assessment in neuronal systems. Once the lead compounds have been selected, we can also use these neuronal cultures for detailed exploration of the compounds' mode of action, including

the analysis of new drug effects on cellular signalling pathways, or on the expression of pathologically relevant genes and proteins.

A wide range of animal models allows the next step: proof of concept. QPS is conversant with practically every route of substance administration, including long-term intracerebro-ventricular infusion and stereotactic brain injection. As an integrated approach to efficacy testing, QPS offers all standard testing systems for assessing behavioral domains and motoric function. We draw on past experience to help clients make the smartest choices for optimal *in vivo* study design, with future treatment protocols in mind.

After the in life experiment, QPS can perform detailed neurochemical testing on brain samples including analysing neurotransmitters and their metabolites and quantifying the expression of relevant proteins. We are also capable of developing and standardizing new test systems, custom-tailored to the requirements of our clients. Finally, our histology department can perform quantitative analyses of drug effects on brain morphology and pathological structures, as well as immunohistochemical tests for the expression of receptors, single proteins, and more.
Integrated efficacy testing means clients will receive a complete overview of the *in vivo* properties of their new compounds, including information on compound safety, and important translational information. This comprehensive picture can lead to early recognition of unexpected properties, suggesting further clinical development with high predictive value. Our longitudinal studies in rodents using high resolution MRI techniques, including functional MRI, allow early *in vivo* assessment of drug effects - for instance, the development of small pathological changes such as amyloid plaque formation in AD mouse brains. Using these techniques, we can gain insight, too, into compounds' effects on neuronal growth and sprouting, on the regeneration of neuronal circuits, or on compound-dependent changes in the blood brain barrier.



Contingent upon the availability of appropriately labelled compounds, our pharmacological laboratories can also study compound-receptor interaction *in vivo*. For this purpose, we offer a wide range of radioactive and non-radioactive investigational techniques, allowing analysis on a cellular level.

The vast experience of QPS' Neuropharmacology Team and our deep understanding of CNS-related drug development, as well as our close collaboration with groups working in other areas of drug development, such as DMPK and toxicology, provide a comprehensive basis for our clients to make informed decisions about their drug development programs.

DMPK

The blood brain barrier limits the transfer of drugs from the periphery. Identifying drugs to treat CNS diseases necessitates special approaches to drug development. In addition, given the overlap between CNS neuromodulators and peripheral neurotransmitters, specific drug design strategies are required to prevent peripheral side effects. The QPS team is aware of these

additional considerations, providing appropriate tools for optimizing clients' drug development programs early on. One such tool is *in vitro* assessment of membrane permeability, which can yield valuable preliminary information about a novel compound's BBB penetration properties.

Various assessment tools are available to determine brain penetration of a compound after peripheral administration including the determination of the brain/blood and brain/plasma concentration ratios, CSF concentrations as a function of time after drug administration, temporal assessment of tissue distribution, including the CNS, using QWBA and localization of compounds in specific regions of the brain, including the target site(s), using micro autoradiography.

In addition to using labelled compounds with high resolution histomorphological techniques, we can also perform localized brain microdialysis to compare a new therapeutic compound's plasma kinetics with its brain kinetics. We are able to correlate how concentrations of a compound changes in brain interstitial fluid, over time, with simultaneous pharmacodynamic read-outs (for example, the activity of secretases).

Toxicology and Safety Pharmacology

QPS offers the full range of regulatory toxicology and safety pharmacology studies in any species. We also have access to various transgenic rodent models, to meet regulatory agencies' criteria for the use of "relevant disease models" in toxicology studies.

One such example is APP transgenic mice with cerebral amyloid angiopathy, used to investigate the vascular effects of anti-amyloid compounds, such as the induction of micro bleeds or micro-edema in the brain. This phenomenon has been recorded only in clinical studies with anti-amyloid antibodies.

In addition to the whole range of safety pharmacological studies such as the Irwin Screening Battery for CNS evaluation, we can provide more sophisticated behavioral assessments complemented by electrophysiological studies like telemetric EEG recording, as needed.

FLEXIBILITY. AGILITY. SPEED.

QPS CUSTOM-BUILT RESEARCH™

QPS' Laboratory Services

Bioanalysis

The tissue kinetics of a CNS drug is crucial: they determine the duration and intensity of its CNS effects. Apart from plasma pharmacokinetics (PKs), mechanisms that govern CNS tissue kinetics include the rate and extent of blood-brain barrier (BBB) transport and the kinetics of processes of distribution and elimination within the brain. Especially important for CNS drugs, CNS tissue PKs may differ significantly from plasma PKs, because BBB transport and brain distribution often do not occur instantaneously or completely. Therefore, CNS tissue PKs should be considered in CNS Drug Development.

Assessing CNS tissue PKs is challenging, since the brain is not a homogeneous tissue, but rather, is composed of many anatomic structures with differing characteristics. In general, the main compartments are: brain extracellular fluid (ECF), brain intracellular space, and cerebrospinal fluid (CSF).

Using a wide range of techniques, QPS laboratories have the latest analytical equipment to measure drug and metabolite concentrations in these areas, in biological matrices such as plasma, serum, CSF, and brain tissues.

Translational Medicine

The major imperative of drug development is to translate insights gained from basic research into new medications. This task is toughest for CNS therapies. Compared with non-CNS drugs, CNS drugs take longer to reach the market and are subject to greater attrition. These difficulties arise principally because of the complexity of the human brain (the cause of many brain disorders remains unknown), the liability of CNS drugs to cause CNS side effects (which limits their use) and the necessity for CNS medicines to cross the BBB.

Because of all these limitations biomarkers for CNS disorders are becoming increasingly important. Biomarkers are, as defined by the NIH, characteristics that can be objectively measured and evaluated as indicators of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention. By this definition, biomarkers can be used for a wide range of purposes. However, to be applicable to large patient populations, biomarkers must be easily accessible by non-invasive means and measurable repeatedly in order to track changes associated with disease progression or response to treatment.

Ideally, a biomarker for a particular disease has a counterpart in animal models, which on the one hand increases the models' predictive value and on the other hand, allows direct translation to clinical application.

The use of established and new biomarkers can certainly help measure drug activity and toxicity at early stages of clinical development. It can also help identify specific patient populations for clinical study enrolment, determine patient stratification for dosing or follow drug effects when other measures are difficult or not sensitive enough to detect treatment-induced changes. In such cases, biomarkers can become surrogate markers for the drug effect.

CNS disease biomarkers are quite variable. They can be quantifiable molecules such as proteins, peptides and lipids. They can also be inherited variations of genes (genetic polymorphisms) or even imaging variables. CNS disease biomarkers are often molecules-mainly proteins or peptides, but sometimes, lipids-that can be analysed in CSF or, better yet, in blood samples. However, biomarkers can also be imaging variables.

Amyloid beta (Abeta) peptides are the main component of amyloid plaques identified in the brains of patients suffering from Alzheimer's disease. QPS has well established biomarker assays for the measurement of Abeta peptides (A38, A40, and A42) in both CSF and plasma samples that have been used to support Phase I and Phase II clinical studies. These Abeta peptides can be measured using a variety of platforms including ELISA, Luminex and Meso Scale Discovery (MSD). Other biomarker assessments, such as the measurement of Tau/pTau protein and inflammatory marker panels, can also be performed by our staff. QPS has participated in a multi-site AD biomarker assay validation and is now a MSD certified lab for Tau and A42 assays in CSF samples, using the MSD platform.

The Apolipoprotein E (ApoE) gene codes for a protein associated with the transport of cholesterol and other fats. Mutation resulting in the ApoE e4 allele is an established genomic biomarker associated with an increased risk for late-onset Alzheimer's disease. QPS has a validated genotyping assay to determine ApoE status that has been used for patient stratification in Phase II and Phase III clinical studies.

Another biomarker for Alzheimer's disease would be the measurement of hippocampal atrophy, documenting longitudinal morphological changes. As another example, *in vivo* imaging of amyloid brain burden has recently become possible using various specific PET ligands (PIB; Florbetapir). Early changes in regional brain metabolism can be tracked using FDG-PET. Also, electrophysiological correlates of specific brain functions are becoming increasingly important markers for aging, requiring sophisticated EEG evaluation or analyses of evoked potentials (e.g. P300). Such biomarkers are important for early diagnosis of certain CNS disorders, so that treatment may be started before functional deficits are detectable.
QPS has long-standing experience monitoring a range of biomarkers, based on well-validated protocols.

QPS' Clinical Services

Early Stage Clinical Research

QPS has built up ample experience in performing CNS drug studies. Over the past decade, we have performed over 200 Phase I and Phase IIa studies involving CNS compounds. In the early stages of CNS drug development, the delivery of potential therapeutics and their actions are often studied in healthy individuals with normal neurocircuitry. Non-invasive imaging technologies such as nuclear molecular imaging, positron-emission tomography (PET) and single-photon-emission computed tomography (SPECT), functional and structural imaging, magnetic resonance imaging (MRI) and magnetic resonance spectroscopy, electroencephalogram (EEG), event-related potentials (ERPs), polysomnography (PSG), pharmacological challenge models, standardized cognition testing, pupillometry, CSF sampling and proof of biochemical mechanism (laboratory biomarkers) can all be used to create baselines for the study of disease states and their therapeutic modulation — the holy grail: targeted CNS therapy.

In some cases, eliciting key aspects of psychiatric or neurological disease in healthy individuals is problematic, but the use of these technologies is a rapid step towards the development of paradigms for patients. Activation of specific neuroanatomical circuitry within

the brain manifests itself as the functional consequence of a drug effect or disease process. The patterns of neuroactivation and their changes are therefore potential markers of both disease state and therapeutic efficacy.

Focusing on the pathological alterations in CNS processing that mark CNS dysfunction in humans enables a top-down approach to the evaluation of drug effects on disease states. The path of traditional outcome-based drug discovery and development can be long, expensive and uncertain. Early knowledge that speeds decision-making about candidate molecules and therapeutic concepts will facilitate the development process by ensuring that if you are to fail, you fail early and fast.

In relatively small populations of healthy subjects, data relating to efficacy (targeted circuits) and side effects can be determined. Indeed, to facilitate the evaluation of drug efficacy, the development of experimental models in healthy subjects for certain clinical conditions is possible. The accumulation of objective imaging data, interwoven with traditional metrics such as safety and tolerability, provides a unique metric that affects go/no-go decisions on novel drug candidates. At QPS, we believe that early-on in clinical drug development, it is essential to integrate several orthogonal sources of information to increase confidence in decision-making by providing an early matrix within which to judge the probability of success.

QPS is also experienced in early clinical studies involving small groups of patients, as for immunotherapy protocols for Alzheimer's disease. These trials are challenging as they entail exacting safety precautions, particularly when active immunization is applied. For example, extensive brain imaging and biomarker studies may be required, but fortunately, these, as well as detailed investigations of vaccine specific immune responses, are within the core competency of QPS. In the case of passive immunization, the QPS image analysis team is also experienced with ARIA (amyloid related imaging abnormalities), which may occur as a dose-limiting side effect.

Phase II-IV Clinical Research

Over the past few years, the introduction of new diagnostic criteria for Alzheimer's disease has changed its study dramatically. According to disease biology and the amyloid cascade hypothesis, brain pathology in this disease occurs years before clinical symptoms are detected. Recent clinical study failures indicate that treatment of symptomatic patients does not "repair" neuronal damage incurred during the prodromal phase. Therefore, the current challenge is to perform clinical studies on patients extremely early in the disease (prodromal), when only very subtle cognitive changes can be detected. While rendering a reliable diagnosis at that stage is difficult, it is essential not to dilute the study population with patients suffering from other diseases. The endpoint in such early studies is usually defined by the number of converters to disease over a prespecified time period, such as 1.5 to 3 years. Clearly, failure in patient selection would invalidate the trial outcome.

FLEXIBILITY. AGILITY. SPEED.

QPS
CUSTOM-BUILT RESEARCH™

QPS is not only aware of these challenges but employs skilled neuropsychologists experienced with sensitive cognitive tests, such as those used to assess episodic memory, and with the latest computer assisted testing batteries. We are highly practiced in training raters for these methods and in scrutinizing study testing results. In addition, QPS maintains contact with leaders in CNS research and is helping to develop new, even more reliable cognitive testing procedures that will improve early diagnosis and enable more sensitive documentation of treatment-dependent cognitive improvement. This field is progressing rapidly, and QPS is among its most experienced CROs.

Another challenge in new study design is the need to provide biomarkers to support the clinical diagnosis. These may range from traditional CSF biomarkers to sophisticated, *in vivo* amyloid imaging using various PET ligands or structural MRI to investigate subtle neurodegenerative changes in regions such as the hippocampus, entorhinal cortex or medial temporal lobe. QPS employs standardized protocols to integrate international multi-centre studies performing such imaging, thus guaranteeing data comparability between sites. For longitudinal documentation of changes in brain morphology, QPS is well-versed in centralized imaging data processing methods, from the evaluation of whole brain atrophy and ventricular size, to the analysis of structures as mentioned above. We can also apply cutting-edge techniques, such as diffusion tensor imaging. Of note, QPS has long been a leader in *in vivo* amyloid imaging, organizing the first such drug trial for AD back in 2005.

The global reach of QPS clinical research services enables the company to support worldwide clinical trials, integrating experienced sites, all with proven records of reliable and fast patient recruitment. Detailed knowledge of country-specific standards of care also informs site selection for each investigation. So far, QPS has enrolled several thousand patients into AD trials, using the most recent protocols for prodromal Alzheimer's disease, as well as selecting for moderate to severe disease. Our close relationship with key opinion leaders worldwide allows QPS to support our clients with the most current scientific thinking. Of course, QPS possesses similar knowledge of other CNS diseases, such as Parkinson's, ischemic stroke and traumatic brain injury.

The QPS team of experienced project managers and competent CRAs delivers seamless customer support from the early stages of clinical trial planning through site selection, investigator training, study initiation, and ongoing monitoring and quality control. Our team is highly conversant with the global regulatory environment; so far, all of our CTAs have been successfully approved by competent authorities as well as by ethical committees/IRBs.

FLEXIBILITY. AGILITY. SPEED.

The pharmacovigilance team closely monitors clinical trial safety and has experience in compliant reporting to various health authorities. Up-to-date clinical trial management software and electronic case reporting ensure a fast database close after last patient out. Statistical analysis of trial data by a huge team of highly experienced biostatisticians, using both traditional and newer, sophisticated statistical methods also hastens the availability of results. In our experience, expert application of these methods early on in clinical trials is important for detecting treatment-related changes that may determine further approval or affect ongoing clinical development strategies. Recognized experts help compile the integrated clinical trial report, including the discussion of the clinical trial's outcome in relation to current, pertinent clinical research data.

QPS' experience and expertise in every stage of CNS drug development, from early preclinical to clinical, enable us to guide our clients toward successful and timely approval of their therapeutics, whether these are small molecules, biologics or medical devices.

QPS Is Committed To Working With You

QPS has extensive experience in supporting CNS Drug Development. We understand the complexities, particularly with respect to managing and conducting global clinical CNS trials, proper bioanalysis, and monitoring the pharmacokinetics of CNS drug candidates. We are committed to working with you personally to advance your CNS product for the benefit of patients worldwide.

Broad Access

QPS provides clients with broad access to our preclinical and clinical development capabilities. Clients also benefit from our experience in preclinical and clinical development of a diverse portfolio of treatment modalities for a wide range of CNS trails indications. Our preferred vendor agreements also provide for the establishment of client-dedicated units within our organization.

Timely Delivery

Partnering with QPS will position your company for success, enabling timely, personalized delivery of your CNS drug candidate portfolio to the marketplace.

TIME IS OF THE ESSENCE IN DRUG DEVELOPMENT.
CONTACT THE QPS BUSINESS DEVELOPMENT TEAM TODAY!

CALL +1 512 350 2827 | EMAIL Infobd@qps.com