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WELCOME TO INVENTIV HEALTH CLINICAL'S NEW BIOANALYTICAL NEWSLETTER.

This newsletter will deliver all you need to know about new and exciting developments within our bioanalytical service offering.

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Read on fellow scientists! »

» TRANSFORMING PROMISING IDEAS INTO COMMERCIAL REALITY

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WHAT'S NEWS IN BIOANALYSIS

PharmaNet/i3 is now inVentiv Health Clinical

inVentiv Health, Inc., offering best-in-class clinical, commercial, and consulting services to the healthcare industry, has renamed its existing clinical research organization (CRO), PharmaNet/i3, to inVentiv Health Clinical. This renaming reflects the closer alignment between the Clinical segment and inVentiv's commercial and consulting services.

inVentiv Health Clinical welcomes back GC-MS/MS Expert Dr. Jim Settlage. Dr. Jim Settlage, Ph.D. has joined the organization as Technical Advisor to both clients and bioanalytical staff. Dr. Settlage brings a wealth of scientific expertise in bioanalysis and biomarkers having over 30 years of experience in the field. Dr. Settlage will report to Dr. George Scott, Vice President of Bioanalytical Services. inVentiv Health Clinical solidifies their commitment and leadership in the field of GC-MS/MS with the recent addition of the Agilent 7000 GC/MS/MS platform to its Princeton fleet.

TECHNOLOGY UPDATE

inVentiv Health Clinical Adds Waters Xevo TQ-S to its fleet for Improved Quantitation and Sensitivity of Insulin Analogs

Liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) is a powerful analytical technique due to its sensitivity and selectivity. It is a widely used method in order to quantitate analytes in biological matrix such as blood, plasma, serum or urine. This technology has been improved in the recent years in order to achieve lower limits of quantitation. In the late nineties, the AB Sciex API 3000 was the most sensitive mass spectrometer (MS) available. Then, the API 4000 was launched with its innovative TURBO VTM source combined with the patented LINAC® collision cell, delivering high performance and high productivity with greater confidence in results. The API 5000, with the addition of the innovative QJet ion guide technology came subsequently, dramatically improving sensitivity by capturing and focusing more ions generated by the efficient TURBO VTM ion source. This newer model pushed the lower limit of sensitivity at levels never attained so far.

The API 4000 and API 5000 are widely used in the inVentiv Health Clinical (IHC) bioanalytical laboratories, being the workhorses of our MS/MS fleet. However, today's sensitivity requirements and the need to quantitate new molecular modalities by LC-MS/MS require a different toolkit. To address these challenges, the new Waters Xevo TQ-S has been added to inVentiv Health Canadian bioanalytical laboratory MS/MS fleet.

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Specifically designed to maximize sensitivity, the Xevo TQ-S is equipped with a larger ion orifice, an enhanced vacuum pumping configuration, and revolutionary StepWave ion transfer optics: a revolutionary off-axis ion source technology. The patented StepWave consists of two ion transfer stages. The design of the first stage ensures that all the ions are efficiently focused and directed up into the second stage. The off-axis design ensures that all the neutral ions are deviated off the system. This new technology drastically increases MS intensities while minimizing background noise.

The new Xevo TQ-S was chosen to support the determination of Insulin analogs in human plasma. Combined with Waters' Acquity UPLC system, we were able to achieve a lower limit of quantitation of 100 pg/mL, while the API 5000 was unable to achieve this level of sensitivity. A signal to noise ratio of 8:1 was obtained at 100 pg/mL in human plasma. Using the new Xevo-TQS, Insulin analogs can be separated from human insulin under specific conditions.

Although the Xevo TQ-S has been, at this point, used by inVentiv Health Clinical for large molecules such as insulin analogs, its versatility makes it also usable for the analysis of small molecules. The addition of new technologies such as the Xevo TQ-S will definitely help push the limits of sensitivity. Moreover, it will now allow us tomeasure the concentrations for compounds that were not sufficiently measurable by the other LC-MS/MS technologies. Combined with the Waters' Acquity UPLC system, the system is suitable for high throughput analysis, which is without a doubt of critical importance to our leadership in the regulated bioanalysis industry.

Increased Sensitivity through GC-MS/MS

Just under a decade and several name changes ago scientists in our Princeton lab began work on a method for the quantitation of several sterol molecules which sponsors had identified as potential biomarkers. These chemicals share their basic structure with cholesterol, the steroid hormones and many, many other endogenous as well as dietary compounds. They are basically hydrocarbons with 20 or so carbons and one or more oxygens or hydroxyl groups. This gives them about the same water solubility as the components of gasoline.--concentrations in the blood are trace level at best. Early efforts involved LC-MS/MS but there were two troubling factors: sensitivity was going to be a challenge but more importantly hydrocarbons with hydroxyl groups typically fragment under MS/MS conditions to yield the original molecule minus a water molecule. Since they all do this, that transition provides little if any selectivity. Because we had substantial capacity and experience in GC-MS/MS we turned our attention to that platform, where derivatization would yield orders of magnitude more sensitivity and capillary GC would greatly improve the chance of resolving the analytes from potential interferences.

This was not the first time that our lab had employed GC-MS/MS for small molecule biomarkers. During the mid 90's this platform was used to develop and validate a method for quantification of various prostaglandins. At the time GC-MS/MS was probably the only option because LC-MS/MS was still in its early stages of development. But over the

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years a number of LC-MS/MS assays for prostaglandins have been reported in the literature. Nevertheless that original GC-MS/MS assay, now more rugged and automated is still in demand and is, in fact, being employed at the time of this writing.

Clients tend to gravitate toward GC when it is available in spite of the greater expense - LC-MS/MS cannot offer the selectivity of the GC-MS/MS platform, and in the case of biomarkers where no blank matrix is available, it is not possible to know if there is enough selectivity. In a recent multi-year program we collaborated with a group of scientists at the Mayo Clinic in a pharmacogenomic/metabolomic study where we measured a number of steroidal hormone biomarkers by GC-MS/MS. Results from that study have now been published and they will likely impact the decision making of oncologists treating breast cancer.

Now we are working with a small molecule biomarker that may have the most widespread application of any biomarker used in drug development thus far. Several years ago attention began to be directed to the oxidative metabolites of cholesterol. - there are a number of them and they play several critical roles; one serves as the starting point for the biosynthesis of bile acids, another for all of the steroid hormones. But the one that has attracted the most attention is 4-beta hydroxycholesterol (4-b OHC). What makes this substance a potentially powerful biomarker is that its synthesis from cholesterol is catalyzed by an enzyme called CYP3A4, which in turn is important because it is also involved in the metabolism of about half of all of the small molecule drugs on the market.

When CYP3A4 is called upon to metabolize the xenobiotic drug, it can be overwhelmed, in which case the body responds by synthesizing more copies of the enzyme. This can be problematic and should at least be monitored, but quantitating CYP3A4 is not practical because it is not found just in the blood. If synthesis of additional CYP3A4 has been induced, additional 4-b OHC may also be synthesized and this can be quantitated as a biomarker for that enzyme induction. This has been observed in our lab as well as others.

For highly selective and sensitive biomarker analysis we continue to use GC methodology.. In our hands we have demonstrated a critical advantage in that this platform has abundant sensitivity (i.e small sample volume) and takes advantage of GC peak resolution. GC-MS/MS continues to lead as the platform of choice for targeted biomarker analysis, and with 20 years of experience inVentiv Health Clinical is the premier provider of GC-MS/MS services in the industry.

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COMPLIANCE UPDATE

Important Impact of GLP Certification

In the regulated bioanalytical world, operating under the principles of Good Laboratory Practices (GLPs) is non-negotiable. By definition, the GLPs apply to the analysis of non-clinical study samples i.e. samples collected from animal species. However, it is expected by regulatory agencies that every bioanalytical study submitted, clinical or non-clinical, is conducted in compliance with the GLPs. In order to assure that, several countries,require that the laboratory used for the bioanalytical phase is certified for its adherence to the GLPs. As such, most of these countries (predominantly in Europe) have established national GLP accreditation programs to certify their laboratories.

Before 2010, no such program was available in Canada or the United States. This was usually requested by the authorities during the final review of the studies and thus caused a delay in the process to approval.

At the end of 2010, the Canadian government, under the umbrella of the Standard Council of Canada (SCC), implemented its own GLP accreditation program. The inVentiv Health Clinical Canadian laboratory, understanding the importance of such a certification, was very quick to request an inspection from the SCC. The first inspection took place in November 2010 and led to the laboratory's GLP compliance recognition in early 2011. The lab was re-inspected at the beginning of 2013 and met again the SCC's GLP requirements with flying colors.

For a CRO targeting the global market such as inVentiv Health Clinical, obtaining and maintaining GLP certification is a great advantage both from a regulatory and business standpoint. For national authorities, it is a testimony of the quality of the work performed. For European pharmaceutical and biotechnology companies it is a reassurance that the GLP adherence of their laboratory of choice will not hinder the progress of their submission. Since 2011, all bioanalytical reports issued from our Canadian bioanalytical laboratory include this GLP certification.

SUCCESS STORY & CLIENT TESTIMONIAL

Bioanalytical Team Beats Client's First-to-File Timelines by 12 hours

inVentiv Health Clincal's Princeton laboratory exceeds client expectations by producing final QA'ed data for 5100 samples just 33-41 hours after sample receipt with 0 failed runs and 91-100% ISR

"It is good to get back to my feet again after the "perfect storm" with our First-to File project and also the first with inVentiv. We have evaluated the performance of the planning, the clinical conduct, the bioanalytical testing, and the final report phases for this project. In all of these evaluations the bioanalytical testing was the one phase of the study

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that was not only accomplished brilliantly, but it also excels its own performance. I join X in thanking you all for your valuable help and support, for your professionalism and dedication to this project. Our ANDA timely filing was energized by your performance and it gives us hope for a First-to-File status. Thank-you inVentiv Team, and I hope to have the pleasure to work with this team again sometime in the near future. You really are a dream team!

Regards,

Director Clinical Operations, X Pharmaceuticals Inc."

DID YOU KNOW

- Did you know that inVentiv Health Clinical's bioanalytical laboratories have been successfully inspected by 20 different international regulatory agencies in the last 5 years?
- Canadian agency (HPFB)
- USA agency (FDA)
- Brazilian agency (ANVISA)
- French agency (EMEA)
- Portuguese agency (EMEA)
- Spanish agency (AEMPS)
- Austrian Agency (AGES)
- Standards Council of Canada (SCC)
- MHRA (UK)

inVentiv Health Clinical has gone Mobile!

inVentiv Health Clinical's has released the first bioanalytical mobile application in the industry.

Our new bioanalytical app puts more than 1000 validated methods at your fingertips.

- ✓ Search or browse assays from your iPhone, iPad or Android device.
- ✓ Inquire about any assay with the touch of a button.
- ✓ Receive news, events and company updates.

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- ✓ Keep tabs on new assays in development.

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WHERE TO SEE US

AAPS Annual Meeting	11/10/2013 - 11/14/2013	Henry B. Gonzalez Convention Center, Booth 3214	San Antonio, TX
EBF - 6th Open Meeting	11/20/2013 - 11/22/2013	Hesperia Tower, Booth TBD	Barcelona

CONTACT US

For more information visit our website at http://www.inventivhealthclinical.com/index.htm

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ABOUT INVENTIV HEALTH CLINICAL

inVentiv Health Clinical, formerly PharmaNet/i3, is a leading provider of global drug development services to pharmaceutical, biotechnology, generic drug, and medical device companies. With 7,000 employees in more than 70 countries, inVentiv Health Clinical offers therapeutically specialized capabilities for all phases of clinical development, bioanalytical services, and strategic resourcing from a single clinical professional to an entire functional team.