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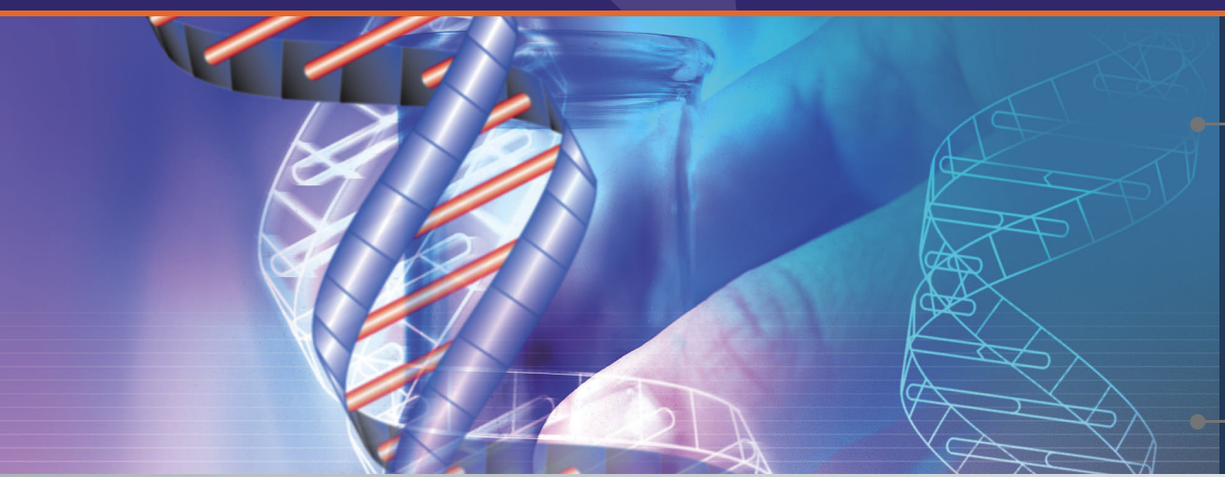

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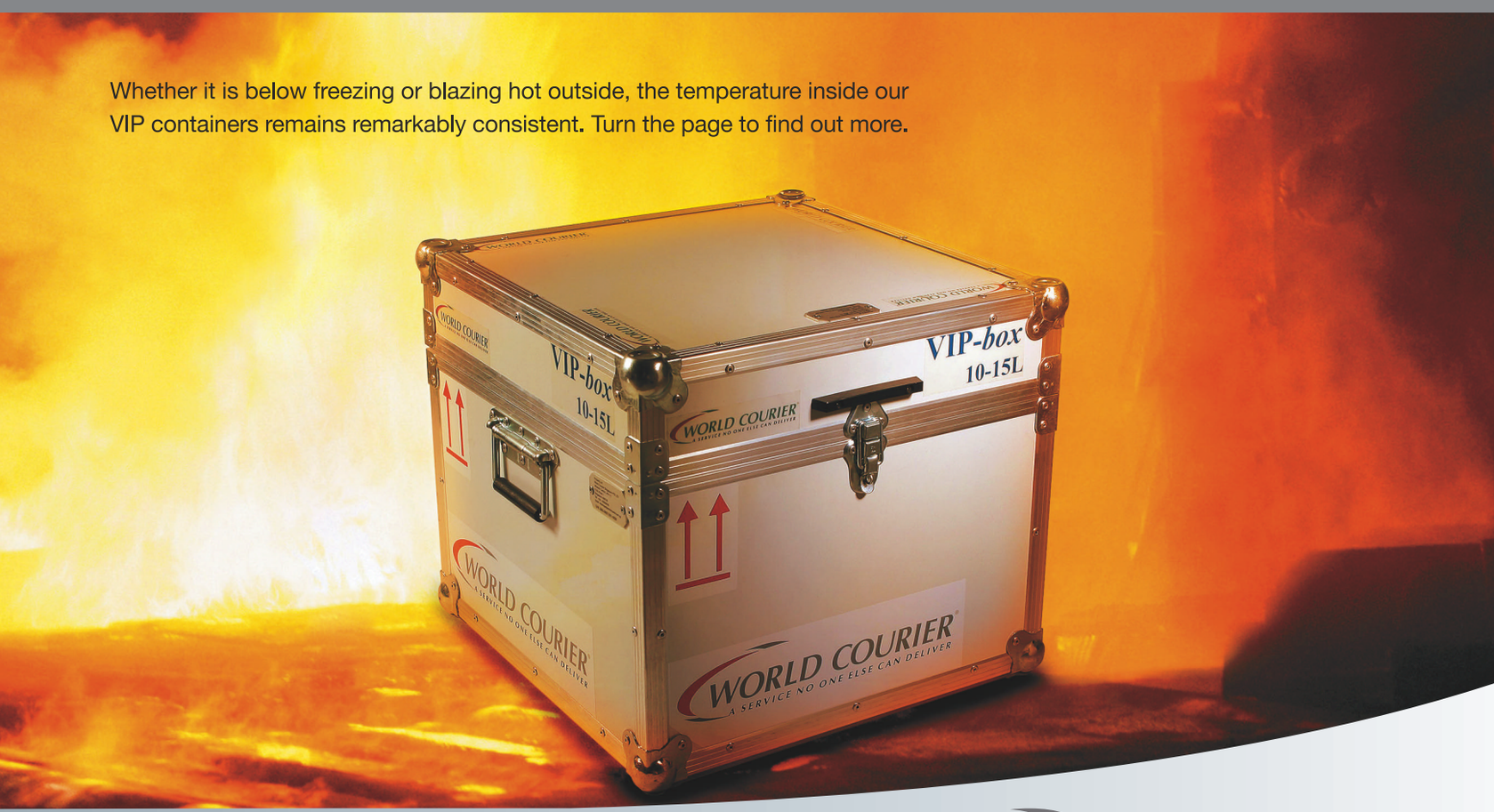

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Drug Development

Data-Directed Detection and Confirmation of Drug

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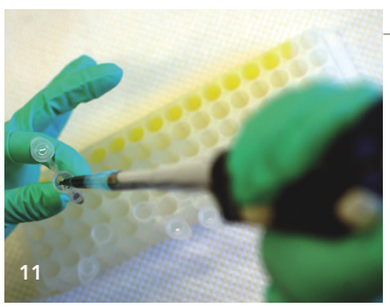

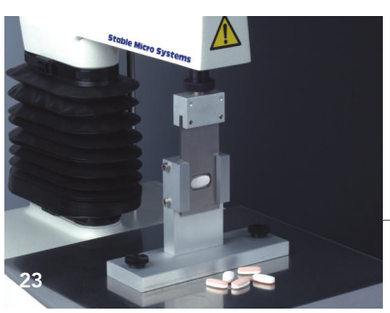

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Editor's Note

Michael Tham
Editor

Time for Change

For many, 2009 could be a time for change. Certainly, economists are warning of a bumpy ride ahead with a slowing world economy and reduced consumer spending. The good news is, however, that Asian governments are stepping up their efforts to cushion the effects.

According to the report by Bloomberg, Singapore Cuts GDP Forecast as Global Crisis Deepens, Jan 2009, various Asian nations have announced spending packages to boost their economies. China has a US$586 billion economic stimulus plan, while South Korea is giving out an $11 billion package of extra spending and corporate tax breaks. The Malaysian government has unveiled $2 billion worth of public projects to stimulate growth.

In the pharmaceutical industry, organizations are turning to creative ways to achieve their goals while reducing overheads. The International Society for Pharmaceutical Engineering (ISPE), a non-profit association of pharmaceutical science and manufacturing professionals, has organized a series of online webinars to reach a global audience – a move aimed at cutting back on the expense of attending seminars in person.

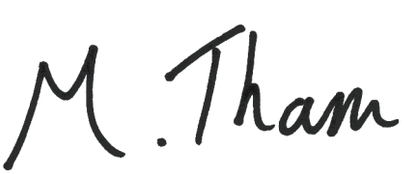
The Singapore government's efforts at developing the bio-tech industry appear to be paying off. The country's biomedical sector saw a growth of 6.2% in November last year, despite shrinkage from manufacturing in most other industry segments (*The Straits Times*, December 27, 2008).

At least one Singapore-based company has much to cheer about. S*BIO is collaborating with Onyx Pharmaceuticals to develop and commercialize the former's JAK2 inhibitors. This gives S*BIO the eligibility to receive up to $550 million in combined equity purchase, option and license fees, and other payments.

Looking further into the future, China's medical sector looks set for further growth. Research Company Decision Resources predicts that the Chinese psychiatric drug market will grow to nearly $1 billion in 2012, through increased social awareness of mental disorders.

At PharmaAsia, we've decided to take on a new direction – a fully electronic publication. Certainly, making the decision to do away with our print copies has been an emotional one. Yet after weighing the pros and cons, we believe that this is a necessary change for us to adapt to the evolving business landscape – and to our serve our readers better.

Coping with change certainly isn't always easy. Yet as one organization has demonstrated, change can provide the stimulus to finding alternative ways for delivering results. Perhaps the current situation calls for putting on the right perspective and pushing on, and to discover better, more innovative methods of getting the job done. **PA**



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Publisher
June Tan, (65) 6780 4304; june.tan@rbi-asia.com

EDITORIAL
Group Editor
Bob Gill, bob.gill@rbi-asia.com
Editor
Michael Tham, michael.tham@rbi-asia.com
Contributing Editor
Sheila Wan, sheila.wan@rbi-asia.com

Editorial Advisors
Eize de Boer, PhD, Global Manager, Life Science Auditing, SGS. **Ian Griffiths,** Medical Director, GSK International Medical, AP. **Jasmin Patel,** PhD, Managing Director, Fidelity Ventures. **Jerold Martin,** MSc, Senior Vice President, Scientific Affairs, Pall Life Sciences. **Lee Babiss,** PhD, President & Global Head, Pharma Research, Roche. **Rama Shankar,** Quality Performance Manager, TAP Pharmaceuticals Products Inc. **Shama Kajiji,** PhD, Director, Portfolio Franchise Management Department, Merck & Co.

SALES & MARKETING
Regional Sales Manager
Alvin Lim, (65) 6780 4521; alvin.lim@rbi-asia.com
Ad Admin Executive
Cyndi Yap, (65) 6780 4816; cyndi.yap@rbi-asia.com

ART & DESIGN
Design Manager
Honess Ho, (65) 6780 4333; honess.ho@rbi-asia.com
Web Designer
Cindy Chen, (65) 6780 4522; cindy.chen@rbi-asia.com

PUBLISHING SERVICES DEPARTMENT
Director
Patti Mo, (65) 6780 4503; patti.mo@rbi-asia.com
Senior Manager, Database and Fulfillment
Zoe Chu, (65) 6780 4536; zoe.chu@rbi-asia.com
Circulation Executive
Levi Cheng, (65) 6780 4869; levi.cheng@rbi-asia.com
Production Manager
Pauline Goh, (65) 6780 4504; pauline.goh@rbi-asia.com

FINANCE
Financial Controller
Lim Suet Ni, (65) 6780 4870; suetni.lim@rbi-asia.com

Managing Director, Reed Business Information Asia
Susie Newham, (65) 6789 9900; susie.newham@rbi-asia.com

Reed Business Information Asia
REED BUSINESS INFORMATION ASIA
The Signature, 51 Changi Business Park Central 2,
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Policy & Projections

Regulation of Chemical Substances in Europe: What it Means for the Pharmaceutical Industry

Carole Garcia
SAFC Supply Solutions

Understanding REACH requirements is fundamental for the trade of pharmaceutical products between the EU and Asia.

REACH is a European Union (EU) regulation that deals with the registration, evaluation, authorization and restriction of chemical substances. It aims to protect health and the environment by identifying the properties of certain chemical substances. A number of the requirements also apply to the pharmaceutical industry.

The regulation has specific implications for manufacturers of substances or articles in non-EU regions, including the Asia Pacific region. Producers and exporters in these regions will be required to register the substances they supply or use for their products, via an 'Only Representative' (OR). Alternatively, they would need to provide European importers with detailed information pertaining to such substances.

Phased Implementation

REACH requires the registration of the existing 30,000 substances produced or imported within the EU. It is a directive that will have a significant impact on transparency and accountability within the global chemical industry.

The regulation requires companies to register any substances imported or manufactured in quantities of more than 1 metric ton per year, with the European Chemical Agency (ECHA). Additional information, including substance toxicological data plus a risk assessment for the various uses of substances, is also required at registration. Establishing which regulations are applicable to the pharmaceutical industry can prove complex, as certain substances used in pharmaceutical processes are exempt from one or more REACH procedures.

In order to facilitate the first-phase of the regulatory implementation, there is a phase-in period for existing substances that will extend their registration timeframe over a 10-year period, to 2018. Substance registration will be prioritized according to the phase-in timeline, based on material volume and hazardous characteristics. To benefit from this phase-in, a pre-registration period ending December 1, 2008 for existing substances was implemented.

Substances introduced to the EU market after 1981 do not benefit from the 10-year phase-in and require registration within 18 months of the date stet the ECHA has been notified of the production, or intended production, of the 1 metric ton per year quantity.

REACH requires the registration of the existing 30,000 substances produced or imported within the EU. (Source: SAFC Supply Solutions)

'Late' Pre-Registration

Following the end of the pre-registration period, companies should assess any gaps in their REACH policies and evaluate potential risk through the documentation of products that have not been pre-registered.

To ensure continuity in supply, companies which import into the EU, or export to Asia from the EU, may find the need to partner with alternative raw materials suppliers that have already registered their products, or have the opportunity to 'late pre-register' them. 'Late pre-registration' can be granted to phase-in substances that will exceed 1 ton per year for the first time after November 30, 2008.

Substances of Very High Concern (SVHCs) is another area that is covered by REACH. The use of these highly toxic substances needs to be known and controlled by the EU. Only about 15 toxic substances have been submitted for authorization. Listed in Annex XIV, to be published in mid-2009 by the ECHA, their use will only be permitted after authorization is granted by the relevant authorities, and is only for applications covered by that authorization for a limited period of time.

Several list revisions are anticipated, with the aim of eventually adding all SVHCs to Annex XIV. In the long term, the plan is to phase out any substance which poses a risk to

humans or the environment within the EU.

The International Chemical Secretariat (ChemSec), in collaboration with leading Non-Governmental Organizations (NGOs) in both EU and non-EU regions, have developed the REACH "Substitute It Now!" (SIN) list, designed to provide an indication of the risk substances that should be replaced.

With the exception of a few high risk materials, such as cobalt chloride, the impact of the current authorization list on the pharmaceutical industry should be minimal. To promote production efficiency, sustainability and cost efficiency, pharmaceutical companies should eliminate the use of SVHCs as early as possible in their drug development processes.

Restriction can apply to all substances, without volume limits. Such substances and their restriction details are described in the current Directive 76/769/EC, which will be replaced by Annex XVII as of June 1, 2009. The new Annex will reflect the same regulatory requirements as the current directive.

Making Exceptions

Many pharmaceutical companies that have evaluated their REACH readiness have concluded that the safest approach is to assume that all chemicals are subject to the regulation, with the following four exceptions:

1. APIs and Excipients – Subject to the regulation but exempt from registration, evaluation and authorization if previously registered with the European Medicines Agency (EMEA) as an ingredient of a medicinal product for human or veterinary use. Only quantities used as registered APIs or excipients will be exempt. But if the same substance is also produced for another use eg, food additives, it is still subject to the regulation.
2. Pharmaceutical Intermediates – Non-isolated intermediates or intermediates produced and kept within a reactor vessel to be transformed into a final molecule or any another intermediate are not subject to REACH. Isolated intermediates must be registered according to different rules and are not subject to authorization procedures. They are also exempt from the evaluation process provided they remain at the production site of origin. Transported isolated intermediates are subject to registration and evaluation.

   Information in the registration dossier of both categories (ie, 'on-site' or 'transported') may be limited to existing information, provided the manufacturer can prove that the intermediates are manufactured and used under 'strictly controlled conditions,' comprising rigorous substance containment, procedural and control technologies that minimize substance emission and any resulting exposure. These conditions must be fully documented and available to the regulatory authorities.
3. Starting Materials and Reagents – All starting materials and reagents are subject to the regulation and must go through the registration process if they are produced or imported in quantities of more than 1 ton per year, per company (ie, per legal entity). Compliance with authorization and restriction requirements is mandatory, even for volumes lower than 1 ton.
4. PPORD Exemption in Drug Development and Clinical Trials – For APIs, excipients, intermediates, starting materials and reagents used during drug development and clinical trials, an exemption can be obtained via a Product-and-Process-Oriented Research and Development (PPORD) notification.

ECHA issues the exemption following the notification, discharging both supplier and user from registering substances produced or imported in more than 1 metric ton per year. This exemption is valid for five years and can be extended for an additional 5-10 years upon proper application. However, even with a PPORD exemption, users must document controlled use and apply health and environmental measures.

In Discussion

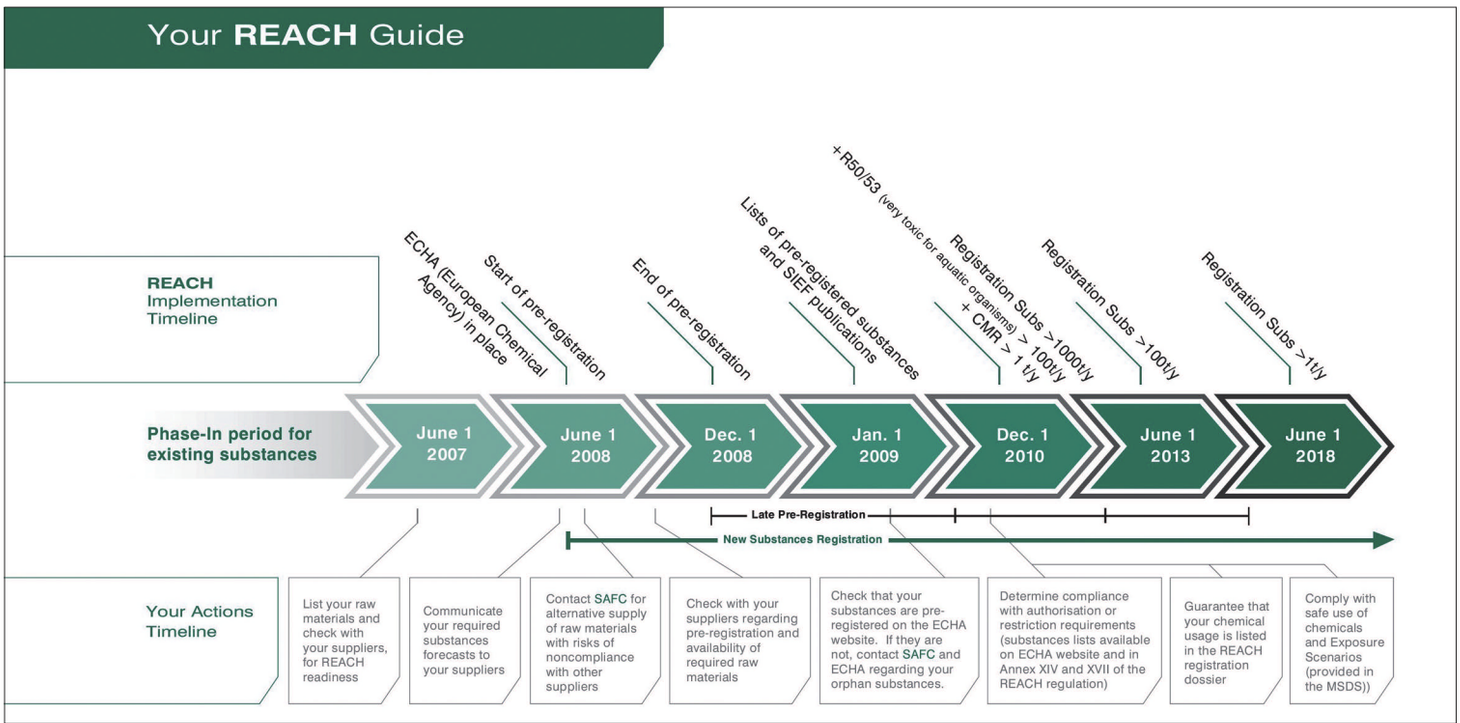
All companies pre-registering substances must participate in a Substance Information Exchange Forum (SIEF), established to encourage greater transparency on substances, in terms of classification, physico-chemical, human health and environmental properties. For Asia Pacific pharmaceutical companies, participation in a forum would be handled by their appointed OR.

Participation continues throughout the entire registration process, allowing for expensive procedure costs to be shared between forum members. Participation stipulates that members exchange product data to prepare a common registration dossier, raising concerns over confidentiality. Pre-registrants may only request not to participate in the forum if there are legitimate reasons such as cost, confidentiality issues or disagreement with a SIEF leader. Declining participation necessitates the submission of a separate registration dossier for substances and the elimination of the longer phase-in period. A full registration dossier must be submitted to REACH within 18 months.

There are concerns within the pharmaceutical industry that the potential short-term impacts of REACH could result in interruption to the supply of some starting materials or reagents that have not been pre-registered by EU suppliers, or by non-EU suppliers that have failed to appoint an OR. The registration procedures may also affect the materials provided by outsourced manufacturing partners.

Previously, products being exported from the EU to Asian markets did not have to fulfill the same criteria as products supplied to the EU. Since the introduction of REACH, this is no longer the case. (Source: SAFC Supply Solutions)

Policy & Projections



REACH Implementation Timeline. (Source: SAFC Supply Solutions)

Investigations into 'orphan substances,' which have not been pre-registered by a supplier but have a user with requirements of more than 1 ton per year, are due to be revealed early in 2009. Substance withdrawal may also be a consequence, as suppliers look to rationalize their product portfolios.

Implications for Asia

REACH presents Asian pharmaceutical companies with challenges. For example, there should be minimal impact on Asian companies which export APIs into Europe, as APIs are exempt from the main legislation. However, if a manufacturer is sending an intermediate to be finished in Europe in quantities of more than 1 ton per year, the product must be registered. Also, as a new substance, the intermediate cannot benefit from pre-registration and needs to be submitted for registration with ECHA within an 18-month timeframe, once 1 ton of product has been manufactured.

Asian companies with suppliers in Europe will also need to ensure that their suppliers and products are now REACH registered. Previously, products being exported from the EU to Asian markets did not have to fulfill the same criteria as products supplied to the EU. However, since the introduction of the regulation, this is no longer the case.

REACH offers Asian businesses a means of simplifying the registration process, as a non-EU manufacturer may appoint an EU-based OR to handle its pre-registration and registration. It is essential that the relationship between the Asian manufacturer and importer is based on trust and confidentiality. Not only will the agent have access to the client's intellectual property (IP) but is also likely to be dealing with the IP of the clients' competitors.

In China, the government carries out an assessment of representatives and advises manufacturers/exporters to use one of its recommended agents.

Establishing which regulations are applicable to the pharmaceutical industry can prove complex, as certain substance used in pharmaceutical processes are exempt from one or more (Source: Dima V)

Asian pharmaceutical companies in the EU supply chain should be prepared to implement REACH, regardless of the volume of critical starting materials and reagents being purchased. Obtaining proof of compliance from EU suppliers may prove difficult, as an official REACH compliance certificate will not be available until the entire registration process has been completed – between 2010 and 2018 for phase-in substances. This underlines the importance for companies to collaborate closely with their suppliers to ensure that appropriate efforts are being made. **PA**

First Phase III Results for FTY720 Announced

Initial results from the one-year Phase III TRANSFORMS study show that the investigational oral compound FTY720 (fingolimod) is more effective compared to a current standard of care for patients with relapsing-remitting multiple sclerosis (MS). It was found that patients on the drug experienced significantly fewer relapses than those treated with the injectable medicine interferon beta-1a (Avonex).

The study, a one-year head-to-head Phase III trial against a standard of care in MS, met its primary endpoint for both doses of FTY720.

The annualized relapse rate at one year for patients given FTY720 0.5 mg was 0.16, representing a 52 percent reduction compared to a relapse rate of 0.33 for interferon beta-1a ($p<0.001$). The FTY720 1.25 mg dose also showed a significant reduction in relapses with a rate of 0.20, representing a 38 percent reduction against interferon beta-1a ($p<0.001$). No statistically significant difference was seen between the two FTY720 doses.

Analyses of the study data are ongoing, and detailed results are scheduled to be presented at a scientific congress in 2009. Regulatory submissions remain on track to be completed in the US and the EU at the end of 2009. **PA**

Activaero Appoints Sole Distributor for Watchhaler

Activaero has announced that the US Pharmaceutical Corporation will exclusively distribute Activaero's Watchhaler, an inhalation concept for children, in the US.

Watchhaler is a reservoir system, or 'spacer', controlling the inhalation flow rate and volume to target the aerosol specifically to the lung region, where the drug is needed. This system is tailored to the needs of children using asthma medications. The child friendly Watchhaler spacer is designed for use with standard metered dose inhalers (MDIs). **PA**

Safe, Nonstimulant Therapies to Treat ADHD

Physicians indicate that there is an unmet need for a safe and effective nonstimulant therapy approved for adult attention-deficit/hyperactivity disorder (ADHD) with no risk of suicidal ideation, according to Decision Resources.

Such a drug has the potential to earn a 25 percent patient share of the drug treated adult ADHD population, according to surveyed US psychiatrists. In contrast, such an agent would earn a higher patient share of 40 percent in Europe, according to European psychiatrists.

This difference likely reflects the US physicians' reasonably high level of satisfaction with currently available psychostimulants, with which they have had decades of clinical experience. This is despite the disadvantages of abuse-liability and prescribing restrictions.

Conversely, European physicians are more averse to stimulants' risk of abuse than their US counterparts, while having to contend with greater prescribing restrictions and fewer treatment options. As a result, physicians would welcome a safer and more effective non-stimulant alternative to Eli Lilly's Strattera as a first-line therapy for adult ADHD. **PA**

Growth Opportunities for Actemra in the Rheumatoid Arthritis Market

Growth opportunities for Roche/Chugai's Actemra (marketed as RoActemra in Europe) will propel Roche to sixth position in the rheumatoid arthritis market by 2012, according to Decision Resources.

One factor is the drug's early market entry into Japan, making it the only agent available for the treatment of inadequate responders to TNF-alpha in Japan until the arrival of Bristol-Myers Squibb's Orencia in 2012. Another factor is the likelihood that the drug will be used in relatively early lines of biologic therapy.

Currently, physicians rely heavily on TNF-alpha inhibitors in early lines of biological therapy, and reserve agents with other mechanisms of action, such as Orencia and Biogen Idec/Genentech's Rituxan (also marketed by Chugai and Zenyaku Kogyo in Japan, and marketed as MabThera in Europe by Roche), largely for TNF-alpha inadequate responders.

According to the report entitled Brands & Strategies: Rheumatoid Arthritis, physicians indicate that Actemra's efficacy data is compelling enough to consider using it earlier in therapy; particularly once it has been on the market long enough to gather some post-marketing data to provide reassurance about side effects such as elevated lipid levels and elevated liver enzymes.

"Despite a recent regulatory setback in the US, physicians are cautiously optimistic about the efficacy of Actemra," said Dancella Fernandes, Ph D, analyst at Decision Resources. It is anticipated that the drug's uptake as a treatment for inadequate responders to TNF-alpha will garner Actemra sales of $603 million in 2012.

The report also finds that despite significant increases in promotional spending coinciding with the launch of Orencia and Rituxan, these relatively new entrants are struggling to secure significant market share in the mature rheumatoid arthritis market.

Promotional spending doubled and increased tenfold (for Orencia and Rituxan, respectively) in 2006 compared with 2005. While Rituxan's spending remained similar in 2007 compared to 2006, Orencia's increased fivefold in 2007. Despite these efforts, only one percent of surveyed rheumatologists reported that Orencia or Rituxan was the first brand that came to mind when thinking of rheumatoid arthritis treatments. **PA**

MiddleBrook Pharmaceuticals to Launch Moxatag in March

MiddleBrook Pharmaceuticals has announced that it will launch Moxatag (amoxicillin extended-release) tablets, 775mg, in March this year. According to the company, the product is the first US Food and Drug Administration (FDA) approved, once-daily amoxicillin.

Moxatag is approved for the treatment of adults and pediatric patients, 12 years and older with tonsillitis and/or pharyngitis. The company also announced the completion of manufacturing validation of Moxatag. **PA**

Arthritis Treatment Drug Receives Recommendation

Nitec Pharma's lead product Lodotra has been recommended for European regulatory approval for the treatment of rheumatoid arthritis (RA) and associated morning stiffness. Germany was the reference member state and the drug is now also considered approvable by the regulatory agencies of 14 other countries (the Euro15) under the Decentralised Procedure

Lodotra is a single-pulse delayed-release (SPDR) low-dose prednisone tablet, which has been developed using SkyePharma's Geoclock technology. The drug has demonstrated a significant long-term reduction in morning stiffness of the joints, and a simultaneous reduction in interleukin 6 (IL-6).

In RA one of the most debilitating symptoms is the stiffness and pain in the joints during the morning hours after waking. These symptoms are caused by proinflammatory cytokines, such as IL-6 which peak during the night and are responsible for the resulting stiffness and pain.

Lodotra is a circadian cytokine modulator (CCM), which can be taken at bedtime. The drug releases the glucocorticoid prednisone at around 2am, enabling suppression of the nocturnal proinflammatory cytokines. This results in an effective relief in the early morning symptoms of RA, in addition to the treatment effects of glucocorticoids.

Anders Härfstrand, Nitec CEO said, "we are well positioned to focus on Lodotra's commercialisation in Europe as well as its ongoing development in the US, and label extension into severe asthma." **PA**

Inauguration of Stem Cell Society Singapore

The inauguration of Stem Cell Society, Singapore took place at the Science Hub, Biopolis, in December last year. Associate Prof Lim Sai Kiang, President of the Society and Principal Investigator, A*STAR Institute of Medical Biology, officiated the event.

The guest-of-honor was Prof Lee Eng Hin, Executive Director, Biomedical Research Council (BMRC). The launch included keynote speeches by two guest speakers: Prof Davor Solter, Senior Principal Investigator in the Institute of Medical Biology and Professor at the Duke-National University of Singapore Graduate Medical School, gave a seminar on the history of stem cell research. Dr Alan Colman, also a Principal Investigator in the Institute of Medical Biology and the Executive Director of the Singapore Stem Cell Consortium, delivered insights on the future of stem cell research in Singapore.

(Source: Vivek Tanavde)

Dr Colman drew attention to the development of techniques, in the last two years, that enable scientists to force a differentiated, or specialized, cell to be driven backwards to an undifferentiated state, akin to a stem cell. This process will in the future potentially allow doctors to utilize a patient's own body cells to treat a variety of disease states. It has led to rapid progress within the field of stem cell research relating to regenerative medicine and will give hope to patients with neurodegenerative disorders or those with damaged heart tissue, for example.

Attendees included the society's members, ranging from graduate students to principal investigators, executive directors of the A*STAR institutes, and directors of major hospitals in Singapore. Guests included representatives from Millipore and Invitrogen, co-sponsors of the event.

In addition to its aim to bring together researchers, clinicians, health professionals, and companies interested in stem cell research and development, the society also hopes to act as a public resource, providing information to lay persons about stem cells.

The key event for the Society will be its first Annual International Stem Cell Conference scheduled to be held in November 2009. Providing a focal point for stem cell researchers in the region, the conference aims to attract major players from the international stem cell research community. **PA**

Proditec Asia: Tablet Inspection System for Lease

Proditec Asia, a manufacturer of industrial vision systems, is offering new services to the Asia-Pacific region. Its automatic tablet inspection alternative to manual sorting for batch recovery, the Inspectab 150, is now available for lease.

This leasing service is catered to solid form manufacturers who wish to inspect and sort tablet batches occasionally, with accuracy and consistency. Turnkey services typically include free-of-charge feasibility assessment, shipping and logistics, full start-up and engineering support, machine operation until full completion of sorting campaign.

According to the company, this technology will typically eliminate from the batch, tablets with dimensional, coating, printing, embossing or contamination defects. Audit trail and reports can be generated as appropriate.

The machine is 21 CFR part 11 compliant, uses FDA approved materials, adheres to Good Automated Manufacturing Practice (GAMP) V4, and is designed for quick set-up and change-over, irrespective of tablet size or shape.

"We believe that Asian customers can reduce their overheads by adopting this technology for occasional sorting campaigns, compared to manual sorting – and without bearing the cost of full capital expenditure," says Chris Bonfils, Managing Director. **PA**

(Source: Proditec Asia)

S*BIO Inks Agreement with Tan Tock Seng Hospital

S*BIO has signed a collaboration agreement with Tan Tock Seng Hospital (TTSH) in Singapore, to evaluate the effects of its JAK2 inhibitor, SB1518, on biological samples from patients with myeloproliferative neoplasms (MPNs).

Its scientists will work with TTSH investigators to evaluate the potential therapeutic effects of SB1518 on diseased blood cells isolated from patients with MPN, and to validate the utility of biomarker assays with these patient samples. The cellular response to drug treatment will be monitored in terms of general viability, specific apoptotic response, specific biomarker changes and JAK2 mutational status. A total of 50 patient samples will be collected for the study, through to the first quarter of 2009.

The TTSH team will be led by Dr Ong Kiat Hoe, a consultant hematologist from the Department of Laboratory Medicine. Co-investigators from the same department include Dr Ponnudurai Kuperan, Dr Lee Lian King, Dr Fong Sing Zern and Dr Chiam Yaw Yung. **PA**

HUGO Workshop in Genomic Sciences

The Human Genome Organization (HUGO) High Content Cellular Screening (HCCS) Workshop was held from November 12-14, 2008 at the Raffles City Convention Centre in Singapore. The event marked the inauguration of a series of workshops on genomic sciences.

The event was attended by representatives from research institutes and academia from the Asia-Pacific region, the Americas and Europe.

Showcased products ranged from cellular and molecular applications, to reagents and labware. Subject areas included chemical analyses, micro and cell biology, computational and analyses of high-throughput data, electronics and technologies of microscopes and cameras.

Sponsors included Research Instruments, BD Biosciences, GE Healthcare and Thermo Scientific. **PA**

Lab-in-a-Cartridge for Disease Detection

Dyamed Biotech has licensed an all-in-one automated diagnostic system called MicroKit from the Institute of Bioengineering and Nanotechnology (IBN). As part of its agreement with Exploit Technologies (ETPL), Dyamed will set up a company – SG Molecular Diagnostics, to develop and produce a range of diagnostic products, based on the technology.

The latter expects to roll out a molecular diagnostic real-time PCR platform called 'MicroKit AIO' as its first product for the global market by 2010.

IBN's device is able to handle a variety of samples, including tissue and body fluids. It is used for the early detection of cancer, avian flu and other infectious diseases. The technology can perform automated gene extraction in six minutes and gene detection within an hour. All the molecular diagnostics processes are carried out in a self-contained, compact cartridge that is preloaded with reagents.

Clinical trials are currently being conducted for the prototype. **PA**

Kendle Expands Asia/Pacific Operations in India

Kendle, a clinical research organization has opened a second office in Ahmedabad, India. The company's operations in India provide customers access to early and late stage clinical development services.

Kendle's expansion in India reflects the growing importance of the country to the global clinical research market. With a population of more than one billion, a growing and improving research infrastructure, an efficient and evolving regulatory setting, and favorable intellectual property laws, India is becoming a world power in clinical research. Analysts estimate that as many as 15% of global trials will be conducted in India by 2011.

"Expansion in the Asia/Pacific region, and India in particular, is essential to our continued success," said Candace Kendle, PharmD, Chairman and CEO. "Our increased presence and capacity in the region will allow us to better meet the needs of our customers who are seeking to capitalize on India's cost-effective, yet high-quality clinical research capabilities to develop their compounds." **PA**

Takeda Pharmaceuticals Asia Appoints CEO

Takeda Pharmaceutical Company has appointed of Stefan Ziegler as CEO of Takeda Pharmaceuticals Asia (TPAsia), to oversee Asian sales and marketing. TPAsia will supervise business activities in Taiwan, Thailand, the Philippines, Indonesia and China. **PA**

Cover Story

Establishing the Standards in Biomarkers Research

Josep Prous
Vice President & Chief Scientific Officer
Scientific Business of Thomson Reuters
Colin Williams
Product Manager, Biology & Bioinformatics Solutions
Scientific Business of Thomson Reuters

Availability of reliable information and the establishment of standards are needed for efficient biomarker development.

Biomarkers look likely to become one of the major drivers in pharmaceutical research and drug development. They have the potential to encourage innovation, improve efficiency, save costs, and gain research organizations an advantage over their competitors.

Increasingly, many decision-makers throughout the development pipeline are turning to biomarker evidence to support their stage gate judgments. This enables patients to benefit from drugs that are more efficacious and have fewer side effects.

However, research organizations currently face a number of hurdles in realizing and passing on these benefits. Regulatory agencies are reluctant to accept biomarker-based evidence to support a drug approval without reliable standards of biomarker documentation.

The Value of Trust

The information provided by a biomarker must be trustworthy if it is to be used to support a key decision. And biomarkers must become established enough that they shift the research paradigm away from the 'blockbuster' model to a smaller market – but with more carefully targeted products.

It is believed that every disease process may have a number of biomarkers associated with it, though the presence of a biomarker by itself may not be useful in clinical practice. To be worthwhile, the biomarker must be a signaling characteristic (ie, a characteristic with a known correlation between the evidential quantity and the disease state) that can be measured accurately, easily and cheaply, preferably using noninvasive techniques such as medical imaging, blood or urine analysis, or gene chips.

Many scientists already use a core set of these biomarkers, but this is insignificant compared to the thousands of biomarkers that may exist and are yet to be discovered, documented or quantified. Even excluding those that are less reliable, or less easy to measure, this suggests a wealth of indicative information that can be employed in every phase of drug discovery, development and clinical practice.

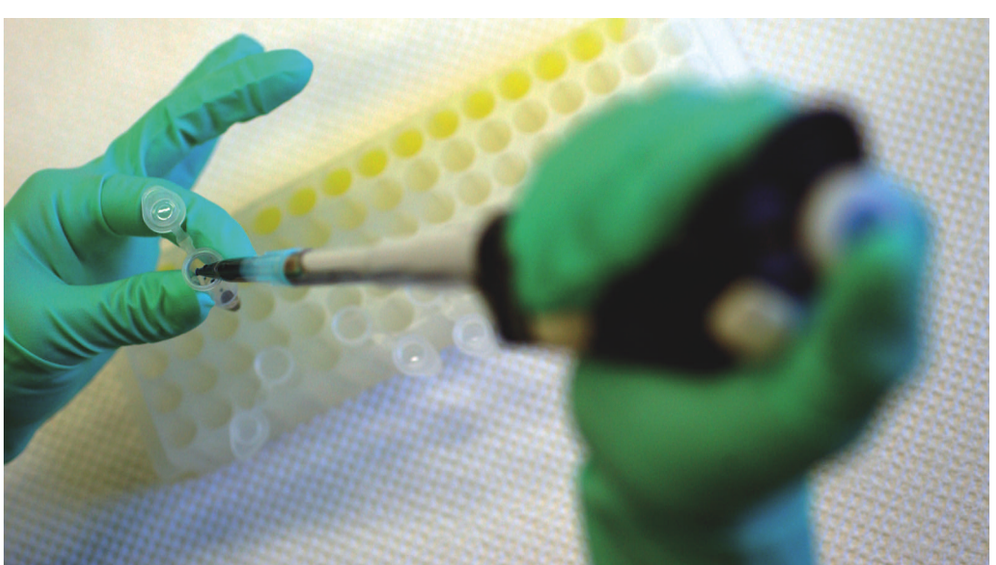
As biomarker research gathers pace, an understanding of the role of these signalers is increasing in therapy areas such as cancer, cardiology, neurology, metabolic, autoimmune and inflammatory diseases.

Biomarkers can provide their discoverers with tangible benefits in terms of speeding up and focusing the development of associated treatments for the disease they indicate. However, most research is proprietary, and biomarkers are themselves commodities just like the drugs they help to bring to market.

Biomarker research, too, follows a similar pipeline to drug research: from discovery, through initial documentation and exploratory use in pre-clinical and clinical development. This is then followed by publication and regulatory approval, and ideally onward into widespread adoption in clinics.

Meeting Objectives

There appears to be as high an attrition rate in biomarker development similar to



The information provided by a biomarker must be trustworthy if it is to be used to support a key decision. (Source: Corbis)

drug development. The end-point for a biomarker researcher may not simply be to support drug development, but to establish and manufacture diagnosis kits and software, along with licensing opportunities.

Of this research pipeline, the key stage is, naturally, regulatory approval. Without the approval of diagnosis equipment by the authorities, a biomarker remains 'non-validated', meaning that it is unusable for clinical practice or to support the claims made during drug development. Even if this is the case, the non-validated biomarker may still be useful in the early proof-of-concept stages of drug discovery and research.

Similarly, even with biomarkers that regulatory authorities are not confident enough to validate, these may still be used in laboratory, biochemical, molecular or physiological tests.

A single biomarker may have different uses, where only some of which are validated. The Her2 biomarker is an established indicator of breast cancer, and is validated for cardiovascular toxicity in patients taking certain drugs. It has however not yet been authorized for ovarian and prostate cancer.

Until now, the association between an intermediary and a disease state seems to be largely retrospective. The role of the intermediary as a reliable indicator is known first, before it becomes established as a biomarker. For example, cholesterol levels are a method of measuring risk for heart disease, blood pressure for stroke or renal failure.

The role of an authoritative biomarker database is to establish standards that can reverse this process: To wrap a wealth of objective evidence that is supported by published literature, around new biomarkers. This is to help the latter achieve validation.

Catch-22

Given their potential benefits throughout the drug development process, biomarkers are still not being adopted universally.

The catch-22 is that while biomarkers remain undervalued by innovators, they will also be undervalued by regulatory authorities. By the same token, while regulatory authorities lack confidence in biomarker evidence, innovators will be reluctant to rely on them to support their stage gate decisions.

Naturally, there are some diseases where biomarker research is seen as less important than others. But even among these, future developments may lead to unexpected and beneficial innovations.

Benefiting from Biomarkers

Bristol-Myers Squibb's use of biomarkers provides an example of three key ways in which biomarkers can benefit pharmaceutical R&D:

1) To differentiate a phase III compound from its generic competition In a selected patient population from a phase II trial involving 161 patients, the response rate to ixabepilone rose from 18 per cent to 45 per cent. This is in comparison with a generic taxane, based on markers of sensitivity identified in studies of 18 different breast cancer cell lines.

2) Line extension of a late-stage drug Dasatinib has been launched in the US and EU for chronic myelogenous leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL), and is in early-stage development for solid tumors. A strong correlation has been observed between solid tumor Src activation profile and patient response to Dasatinib.

3) To improve the risk-to-benefit ratio of an existing therapy Markers to predict incidence of lipodystrophy induced by highly active antiretroviral therapy (HAART) include an alteration in the resistin gene (coding for an adipocyte-derived hormone linked to obesity and diabetes), which has been associated with high risk of lipodystrophy.

For example, if a researcher is working on defining the genetic basis of hypertension, the genomic aspects of that disease will be critical. This is especially true if a biomarker that indicates which patients are likely to respond to which types of therapy, can be found.

The availability of trusted, validated biomarker information may pave a way out of the catch-22 situation, by providing opportunities:

- Biomarkers can be used to detect the predisposition for disease in a population, screen for its presence and confirm its diagnosis. They can also assess its severity, predict its response to available therapies, and measure its clinical course.
- Biomarkers can be used as targets to discover new drugs. They provide improved systems for screening a library of compounds for promising candidates and decreasing the number of false results.
- The existence of viable biomarkers can be a decisive factor in determining whether or not to continue research on an entity, particularly at the proof-of-principle and proof-of-mechanism stage gates.
- Biomarkers can indicate early in the development phase, whether an entity could lead to side effects that should terminate further research. This can help reduce the attrition rate further down the pipeline and minimize risks. It is estimated that as many as 1.5 million patients are hospitalized each year due to the adverse effects of prescription drugs.
- When it comes to clinical trials, biomarkers can help to make efficacious decisions that save time and money, for example by identifying suitable subjects for initial human testing. They can also provide data sooner, with objective reliability. For example, an anticancer drug could be tested against tumor growth or progression-free period, rather than mortality.
- Biomarkers can reduce treatment overheads by optimizing dosage and measuring a patient's response more quickly and accurately. This in turn may introduce the need to measure additional biomarkers, more closely targeting the therapy to the individual patient.

These are tangible rewards for both innovator and patient, as well as a third beneficiary: the payer. As the analysis suggests, if the majority of prescription drugs only work in less than half of the patients who receive them, clinicians are wasting health authority or employer insurance scheme monies on ineffectual treatments. This could easily amount to several hundred billion dollars each year.

Meanwhile, cost pressure on those same payers means regulatory bodies will only approve drugs that are shown to be more effective than the established treatments. It

is the regulatory bodies that ultimately need to be convinced by biomarkers.

Seeking Approval

During the early stages of drug discovery and development, a pharmaceutical organization can use whatever biomarkers it feels are most reliable. This is regardless of whether or not they have been validated by regulatory agencies. This is also true, to a lesser extent, during phase I and II clinical trials, so long as the biomarkers are ethically acceptable.

Later, when the candidate approaches phase III trials, the organization has no choice but to switch to those biomarkers that will be accepted by regulatory agencies as evidence for approval.

In other words, if a regulatory agency accepts one biomarker as valid for establishing efficacy, but does not accept another, it is in reality supporting research in some biomarkers but not in others.

The suspicion is that, whatever their intentions, the regulatory agencies may be exacerbating the paradox of biomarker research. Since very few of the biomarkers that have the potential to be used as indicators of efficacy or toxicology in trials have yet been validated to the standards of the Food and Drug Administration (FDA) and other agencies, the confusion threatens to stifle research altogether.

Nevertheless, the stated position of the FDA is to encourage and support biomarker research, suggesting that the appropriate inclusion of biomarker evidence is likely to speed up approval.

In its Critical Path Opportunities Report, March 2006, the FDA endorsed the importance of biomarkers. It declared taking the lead in trying to establish a regulatory framework that could expedite incorporation of biomarkers into the development process. However, it also noted that "much development work and standardization of the biological, statistical, and bioinformatics methods must occur before these techniques can be easily and widely used."

By claiming that biomarker research had "stalled", the FDA was actually highlighting its own barrier to regulatory acceptance of biomarker evidence. The authority rarely has an issue accepting biomarker data as evidence of a secondary clinical endpoint, but accepting them as evidence of a primary endpoint is a quite different matter.

If the state of the art is to assess efficacy by looking at a biochemical or physiological or molecular endpoint, the FDA generally rejects it as a satisfactory clinical endpoint for approving the drug to market. It tells the innovator that the primary endpoint must be clinically relevant to the disease and the patient's well-being.

Seizing the Initiative

The FDA does recognize that biomarkers are an area of importance to pharmaceutical innovation and personalized medicine, and is making efforts to build a framework for regulatory acceptance. Other agencies, including the European Medicines Agency (EMEA), are engaged in the same issue.

In Japan, the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labor and Welfare have proposed biomarker development as a national project, and are actively promoting biomarker research.

For example, they have announced a program to investigate Beta-42 Amiloid approaches to Alzheimer's disease, and are seeking a compound related to salivary amylase and peroxidation in fat as a biomarker for stress. Recent history shows that biomarker research can be accelerated to swift approval where the need arises. With minds sharpened by the AIDS pandemic, it took only a few years of intensive searching for a biomarker to combat HIV, to accept CD4 cell counts as a validated primary endpoint.

Once a biomarker approaches or achieves validation, there is no lack of interest from pharmaceutical researchers to further develop and employ it, particularly if the biomarker may be able to gain more rapid acceptance of the marketing applications of their own candidate drugs. Physicians will also want to use biomarker diagnosis as soon as practicable, particularly if that diagnosis is simple (eg, a lab test of blood or urine samples) for a relatively common disease.

The biomarker PSA, used to assess prostate function, is an example of one such diagnosis that moved rapidly from introduction to widespread adoption in the clinics.

The fast-track biomarkers however, are exceptions. If gaining biomarker acceptance is perceived to be an uphill battle, taking years and millions of dollars, and faced with the challenges of getting approval from regulatory agencies, researchers are likely to tire of the effort. The trend may then be to shift focus elsewhere.

Meanwhile, no single innovator is likely to step forward to take the entire weight on its shoulder, as this is a fiercely competitive commercial industry where each organization works independently of its rivals. Many companies state that they have no intention of coordinating their efforts with others. The academic field is not likely to take the lead either.

It therefore falls to an objective outside body to seize the initiative.

Evolving Information Into Knowledge

There is no lack of biomarker information already in the public domain, and more is being released on a daily basis. But little of this has the level of trust and authority necessary to provide the evidential framework needed for biomarker validation by the regulatory agencies. Neither is it sufficient to support stage gate decisions by innovators that may cost, save or generate millions of dollars for their organizations.

Furthermore, the information is unable to evolve into knowledge when there is a lack of effort to standardize the vocabulary. To date, the existing commercial sources have also not taken a lead in the area, either due to a lack of resources, industry expertise, content depth and breadth, or editorial rigor.

Simply identifying and documenting new biomarkers is not the issue. What is more important, and difficult, is compiling the data from all its disparate sources into usable formats, and then comparing the relative values of each biomarker that can be used to determine the same effect or physiological activity.

Researchers must learn from the database, the degree to which they can trust the biomarkers to support their work.

An ideal biomarkers initiative needs to be based on in-depth interviews with a number of pharmaceutical, biotechnology and diagnostic companies, talking to both senior management and business development specialists, and the front line of discovery at the bench.

A database (eg, Thomson Reuters' BIOMARKER center) should form a repository of knowledge covering the different uses of biomarkers that are actively being researched or employed. It should incorporate those uses that have been discontinued.

Each record includes the biomarker's name, classification, biological entities/processes involved, associated drugs, roles or utilities, measurement techniques, development status of diagnostic kits and validation status. It places this knowledge in context, enabling users to assess at a glance the relative importance of different biomarkers. It also indicates how much an organization can put its trust in the biomarker results it is getting.

Supporting contextual information for core biomarker data includes related literature, patents, genomics/targets, drugs and biologics, companies or research institutions, toxicology and clinical studies. The database enriches each record by retrospectively searching the literature and providing links to all source documents. **PA**

An Intermediary Between Treatment and Disease

'Biomarker' is a good example of a term whose dictionary definition is not keeping pace with the word's changing significance in the real world. Originally, it referred to such physiological indicators as body temperature, blood pressure or heart rate that signaled an imbalance in the body—direct, evidential symptoms of disease. Later, the term took on the additional meaning of detectable foreign substances such as radioactive isotopes whose passage through the system could indicate problems with specific organs or body functions.

Today, a biomarker can more precisely defined as a blood-based test, gene sequence or mutation, mRNA expression profile or tissue protein that can be used to provide evidence of the state of an organism.

The US National Institutes of Health Workshop in December 1998, published in Biomarkers And Surrogate Endpoints: Preferred Definitions and Conceptual Framework (Clinical Pharmacology & Therapeutics, Volume 69, No 3, 2001), calls a biomarker "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention." The presence of a specific antibody in the blood, for example, might indicate a specific infection. The important point is that the biomarker is both objective and measurable.

Once the association between the biomarker and the disease is clearly established, one can be used to signal the other, to a high degree of certainty. Changes in the prevalence of a biomarker in the organism can immediately and reliably signpost the patient's response to treatment, whether beneficial or toxic.

In preventative medicine, by monitoring their blood glucose levels, diabetics can manage their disease and avoid exacerbating its symptoms: the biomarker is an intermediary between the disease and the patient's behavioral regime.

Supporting Biomarker Development with IT

Rohini Srinivasan
Senior Consultant
HCL Technologies.

Information technology plays a vital role in the advancement of biomarkers for drug discovery and personalized medicine.

High clinical development costs and declining drug discovery success rates, pose a potential threat to the pharmaceutical sector. The US Food and Drug Administration (FDA) has taken initiative to address the rate of attrition in innovating new chemical entities by encouraging the use of modern technologies like pharmacogenomics, transcriptomics; proteomics (polyomics).

The global biomarkers market is projected to reach about $15 billion by 2010, with the US retaining its dominance. Asia Pacific is a vibrant region while some of the leading biomarkers companies are in Europe. Cardiology is projected to be the fastest growing therapeutic area of biomarkers during the analysis period 2005-2010 with a compound annual growth rate (CAGR) of 22.3% followed by neurology and oncology.

Bioinformatics is projected to be the fastest growing discovery technology for biomarkers for the same period, with a CAGR of 22.8% followed by genomics and metabolomics (Market Research.com, January 2008).

Issues in IT

The focus of drug discovery appears to be shifting toward biomarkers and personalized medicine. This has given rise to the need for automation, data storage and the collaborative efforts of IT. In addition, pharmaceutical companies are trying to incorporate biomarker data in the submission of new drug applications to FDA.

IT challenges include:

1. Efficiently managing data from disparate sources and data formats (images, data from high throughput technologies and final from external vendors)
2. The Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) requires two additional domains (pharmacogenomic data and imaging data) for the inclusion of biomarker information submission data sets. This calls for an end- to-end IT solution for managing collaborative biomarker-based drug development for submission and review.

Biomarkers enable the early diagnosis and guidance to molecular targeted therapy. They are also used for monitoring the variety of therapeutic responses for various diseases. A need for knowledge system has become necessary because of the following difficulties:

1. the lack of systematic organization – data is decentralized and published in different locations
2. data presentation is not uniform across datasets
3. an increase in both the complexity of data and the number of variables
4. incomplete datasets
5. unpublished data
6. a lack of interoperability issues among datasets
7. non-uniform taxonomy and definitions

Despite growing interest in biomarkers, there has been a decline in new discoveries. This is due to a lack of web-based solutions that can efficiently process and retrieve information pertaining to a specific biomarker of interest.

Providers of IT solutions need to develop data architecture to support the creation of biomarker metadata. It is also necessary to find approaches to create common data elements, data dictionaries, and standards – while at the same time coordinating biomarker knowledge system development with other information and standards organizations.

For example, HCL is an IT solutions provider in India that is developing a web-based solution that retrieves data from various portals. Biomarker data is manually extracted from journals and an intuitive text mining approach will be implemented to organize information from public sources. This can be further integrated with the in-house database, and customized for clients.

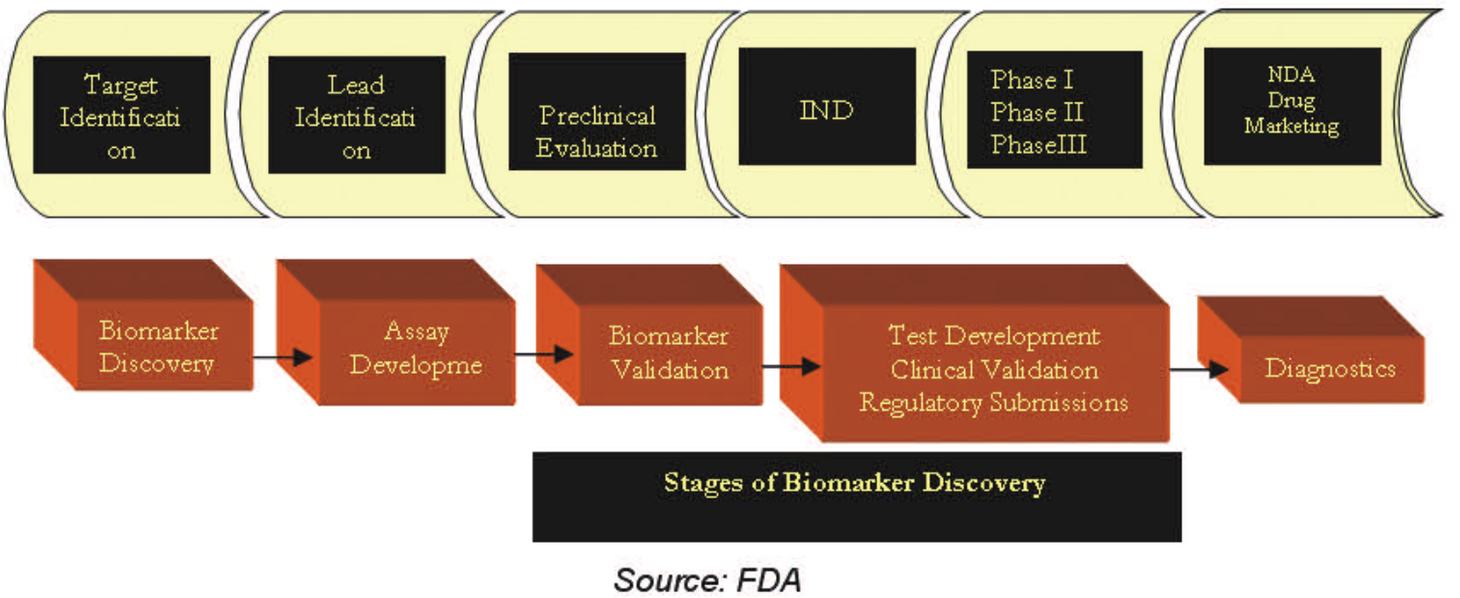
Drug Development

The pharmaceutical industry is looking for a transformation to reduce failures in new drug discovery in terms of technology and research. A decreasing number of new chemical entities (NCE) in the pipeline and an increasing number of drugs failing (in preclinical and clinical stages) are some of the challenges faced by the industry. Other issues include a steady rise in the total cost of clinical development, and later stage failures, eg, post-marketing.

There has been a reduction in new chemical entities entering into the drug development cycle. This is due to a lack of efficacy and an increase in toxicity and adverse events. The goal of any drug discovery activity is to achieve efficacious, effective responses to dose and early detection of adverse events in the patient population.

Many drugs are only effective in 40-60% of the patient population. There is therefore an increased expectation in personalized

Drug Discovery



Application of biomarkers in drug discovery and development. (Source: FDA)

Stage of Development	Uses of Biomarkers
Pre-discovery	Study of disease mechanism
Discovery	• Define and validate drug targets • Mechanism of action of drugs • Establish structure-activity relationships (SAR)
Pre-clinical	• Build PK/PD models • Mechanism of action of drugs • Safety and efficacy end points • Guiding compound selection and retention
Early Clinical	• Bioequivalence • Dose response • Mechanism of drug action in humans
Late Clinical	• Define the target population • Dose selection and optimization
Marketing – Post Marketing	• Marketing – Post Marketing • Monitor therapeutic response Side-effects

Biomarkers in various stages from discovery to post-marketing.

medicine to provide increased efficacy and reduced adverse side-effects. This has given rise to greater pressure for innovative and novel methods in determining explicit drug targets.

Biomarkers play an important role in personalized medicine and have gained importance in drug discovery where they may be used as a predictive method in detecting dose responses.

Current information on biomarkers comes in the form of human genes, genetic variation ribonucleic acid (RNA), proteins and metabolites.

Transcriptomics provides a greater impact on target-based discovery by profiling the expression patterns of thousands of genes and biological mixtures. The first stage of biomarker discovery depends on analytical instruments' techniques that involve mass spectrometry. This is to perform unbiased semi-quantitative analysis between normal and disease states.

The next stage is biomarker validation and clinical assay development. This depends on high throughput sensitive immunoassays. It is among the greatest challenges in biomarker discovery specific to the clinical state and related to the disease state or toxicity.

The techniques used in the discovery of biomarkers are: genomics, proteomics, transcriptomics, metabolomics and biostatistics.

Biomarker-based drug discovery development appears to be a growing trend. Many pharmaceutical companies are shifting from the classical method of discovery to biomarker-based drug discovery. The development of a multidirectional approach in translational research (polyomics) seems to be making progress.

This effort however, requires collaborative IT architecture support for managing data, applications used for high throughput technologies, data analysis tools in collaboration with biomarker development submission, and for validation and review with FDA. **PA**

Data-Directed Detection and Confirmation of Drug Metabolites in Bioanalytical Studies

Paul Rainville
Rob Plumb
Waters Corp

Speed and accuracy in analysis of biological compounds aids faster drug discovery and development.

Liquid chromatography-tandem mass spectrometry (LC/MS/MS) analysis is an analytical method for the accurate quantification of pharmaceutical compounds or active metabolites in biological fluids. The specificity and selectivity provided by tandem quadrupole MS in multiple-reaction monitoring (MRM) mode allows for rapid high-sensitivity analysis, often in the pg/ml range. Data produced by the analysis provides drug concentration data that is critical to successful drug discovery and development.

Speed Test

Recent US Food and Drug Administration (FDA) guidance, "Industry Safety Testing of Drug Metabolites," provides recommendations on when and how to identify and characterize drug metabolites whose nonclinical toxicity needs to be evaluated. The aim of the guidelines is to ensure that variations in metabolic profiles across species are both quantitatively and qualitatively measured.

In survey scan mode, LC/MS/MS can be used to quickly detect drug metabolites using a common diagnostic fragment ion.

For the experiment, rat plasma was spiked with ibuprofen and related major metabolites. Samples were then precipitated using 2:1 acetonitrile to sample (v/v). The sample was evaporated to dryness and reconstituted in 9:1 water/methanol (v/v). This was then injected onto the UPLC/MS/MS system (See Table 1 for the LC/MS experimental conditions).

The system produced extremely narrow peaks of 2 seconds or less at the base. This required a fast data capture rate mass spectrometer to accurately define the peak. Figure 1 shows the MRM peak for ibuprofen using the transition m/z 205 to 161. The peak is 1.2 seconds wide

LC system:	Acquity UPLC System
Column:	Acquity UPLC BEH C_{18} Column 2.1 x 50 mm, 1.7 µm
Column temp.:	40.0 °C
Flow rate:	600 µL/min
Mobile phase A:	0.1 % NH_4OH
Mobile phase B:	Acetonitrile
Gradient:	5% to 95% B/2 min
MS system:	Xevo TQ MS
Ionization mode:	ESI negative
Capillary voltage:	2000 V
Cone voltage:	15 V
Collision energy:	7 eV

Table 1: LC/MS Conditions

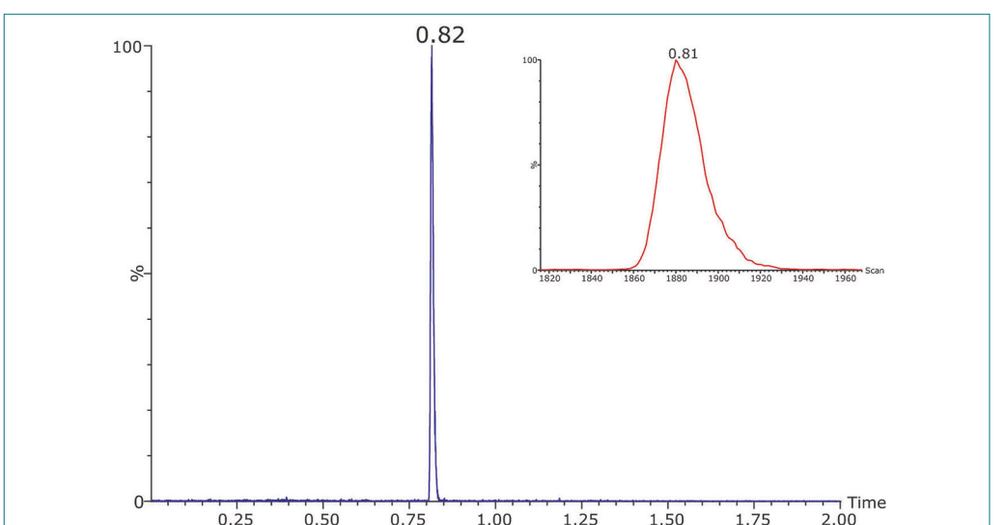


Figure 1: Ultra performance liquid chromatography-tandem mass spectrometry (UPLC/MS/MS) of ibuprofen using the MRM transition m/z 205 to 161.

Drug Development

at the base and the high data capture rate allowed for more than 60 scans across the peak. This facilitated the accurate definition of the chromatographic peak, even if several MRM transitions are employed during analysis.

The recent FDA guidelines recommend that during human clinical trials, the concentration and identity of any metabolites with an exposure of greater than 10% of the dosed compound must be determined.

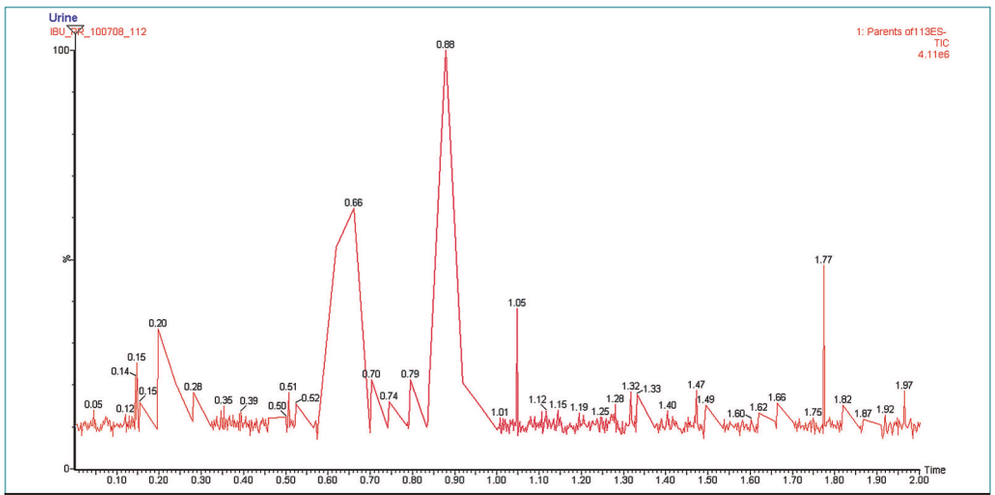


Figure 2: Precursors of m/z 113 switching to product ion scan.

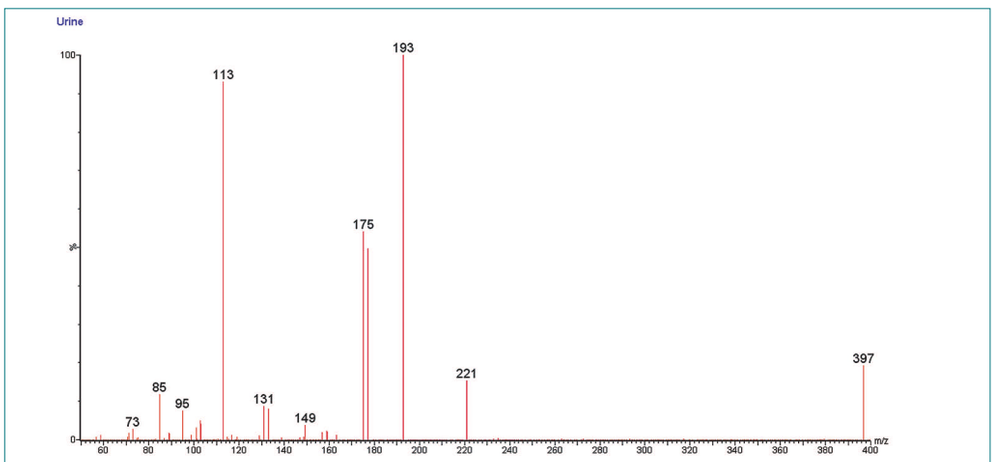


Figure 3: ScanWave DS spectrum of peak eluting at 0.66 minutes.

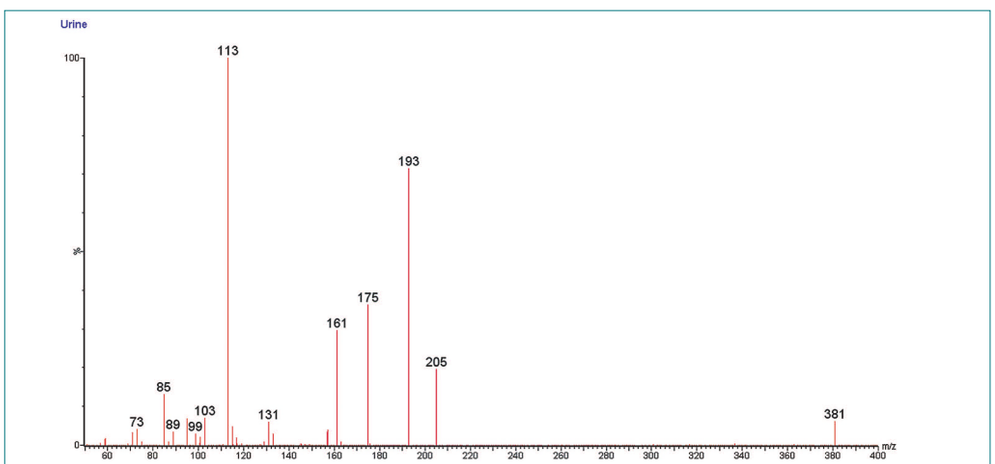


Figure 4: ScanWave DS of peak eluting at 0.88 minutes with a m/z value of 381.

Scanning Possibilities

To this end, mass spectrometry can detect and identify drug metabolites by various means. For example, one method is to utilize a survey scan mode in which the MS is set to monitor a diagnostic fragment ion from the parent drug compound.

The use of a common fragment ion requires the mass spectrometer to scan the first quadrupole (Q1) while monitoring for a fixed m/z with the final resolving quadrupole (Q3). Ibuprofen gives rise to several distinctive product ions, m/z 113, 133, and 161. Figure 2 illustrates Xevo TQ MS operation in survey scan mode.

In this example, the common fragment ion of m/z 113 was monitored by the resolving quadrupole. When a peak containing a m/z of 113, was detected, the MS switched to collect product ion data on the precursor ion containing the m/z 113. Peaks that exceed a user-defined detection threshold are used to trigger the acquisition of product ion data.

Figure 3 illustrates the MS/MS spectra obtained for the peak detected at 0.66 minutes. In this example, the precursor peak m/z value is 397. This produces major fragment ions at m/z 113, 175, 193, and 221.

The m/z values and MS fragment pattern confirm the identity of this peak as the O-glucuronide metabolite of ibuprofen. The data acquired for the peak eluting with a retention time of 0.88 minutes are shown in Figure 4.

This peak was determined to have a m/z value of 381. Resulting fragment ions produced from the product ion MS/MS were m/z 113, 161, 175, 193, and 205. This data set confirmed that this peak was related to ibuprofen. With the precursor ion m/z value of 381, it was confirmed as the glucuronide conjugate of ibuprofen.

It was therefore determined with one experiment, along with the knowledge of the fragmentation pattern of the ibuprofen that the metabolites could be detected and the structure confirmed.

In conclusion, the quantification of pharmaceutical compounds in biological fluids is a regulatory requirement as part of any new drug submission, eg, Investigational New Drug Applications (IND)/Clinical Trial Exception (CTX).

More recently, these regulations have required that drug metabolites with an exposure greater than 10% of the active pharmaceutical be quantified and characterized. The Xevo TQ MS that was used can perform data-directed MS/MS experiments, allowing metabolite structural confirmation using common fragment ions within an ultra performance liquid chromatography (UPLC) peak timeframe. **PA**

Early Detection in Drug Production

Kazutomo Yokoya
Kdm Communications
Bedford, UK

Rapid molecular methods provide timely contaminant detection in biopharmaceutical manufacturing.

Contamination can occur at any stage of the biomanufacturing process and from a variety of sources. These include raw materials, equipment, laboratory personnel and contact with infected substances. Biopharmaceutical manufacturing therefore requires stringent controls in order to detect and eliminate contamination. This is to ensure that products are safe, efficient and of high quality – reducing the overall product risk.

Adhering to Standards

National and international regulating bodies recommend stringent testing standards during biopharmaceutical manufacturing to ensure the delivery of a safe product. The breakdown of contamination control and prevention procedures can be costly for pharmaceutical companies, in terms of both time and money.

The consequences include reduced product quality and safety, uncertainties in the production process, and financial risk to the company through product delay or more significantly, the need for a recall. Awareness of the necessity to improve contaminant and impurity analysis in drug manufacturing has significantly increased due to a number of high-profile recalls of vaccines and other pharmaceutical products.

Biopharmaceutical companies are responding to the challenge, especially for products produced in cell culture, by implementing in-process contaminant and impurity analysis – with the goal of early detection to avoid expensive downstream loss of product. In particular, rapid molecular methods for detecting mycoplasma contamination in mammalian cell cultures, which are difficult to identify and control, are gaining increasing attention in pharmaceutical manufacturing.

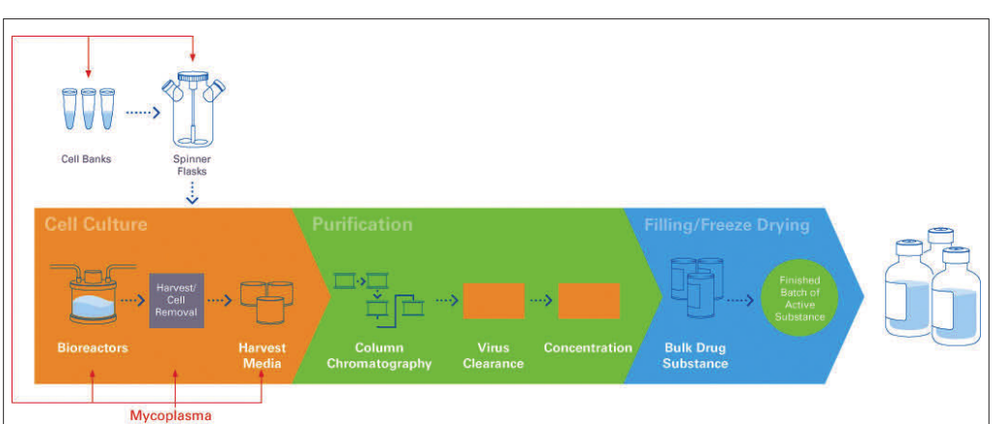
Mycoplasma are prokaryotic microorganisms lacking cell walls. They are therefore resistant to many antibiotics, and have proven to be troublesome contaminants of animal cell cultures. For this reason, detection tests are routinely performed on bioreactors, harvested cells and harvested media. The tests are carried out during the cell culture stage of biopharmaceutical manufacturing, before filtration, purification and final drug formulation.

Contaminant Detection

However, cultures contaminated with mycoplasma show no visible signs and are impossible to identify under a light microscope. This makes them difficult to detect via traditional methods for contaminant detection based on phenotypes. Furthermore, traditional culture methods to identify these microorganisms can take as long as four weeks, delaying the availability of critical information needed for effective decision-making.

The industry has been calling for new technology and methods that offer same-day results and real-time testing during the cell development process. Analytical companies are beginning to respond – regulators and pharmacopoeias are increasingly turning to rapid molecular methods, which are emerging as the gold standard for contaminant and impurity analysis performed in biopharmaceutical manufacturing. In addition to the traditional phenotypic methods, newer molecular, DNA-based approaches to contaminant and impurity analysis are now available, designed to meet regulatory guidelines.

Scientists are increasingly adopting these rapid molecular methods to detect and



The biopharmaceutical manufacturing flow. The cell culture stages of biopharmaceutical manufacturing processes are vulnerable to contamination by mycoplasma. Arrows indicate the steps that require routine testing for mycoplasma contamination. (Source: Applied Biosystems, a division of Life Technologies)

Drug Manufacturing

identify tiny amounts of potentially harmful microorganisms that cannot be quickly detected by traditional technology.

Applied Biosystems has a rapid molecular method for the detection of mycoplasma. It is based on real-time polymerase chain reactions (PCR) – a common laboratory method used to simultaneously detect and determine the amount of DNA present in biological samples.

Purification Process

Firstly, the DNA is extracted and purified using a magnetic bead-based protocol; starting samples can be from 100 µl to 10 ml of cell culture, containing up to 108 cells. The purified DNA is then combined with the assay mix along with the Power SYBR Green Master Mix.

Finally, the resulting reaction mixture is run on a real-time PCR instrument, alongside negative controls. Results can be obtained in as quickly as half an hour. Real-time PCR can detect as little as a doubling of the number of DNA copies present, for example from 10 to 20.

It collects data during the exponential phase of the reaction when amount of PCR product exactly doubles after every cycle and where the reaction is specific and precise under optimum conditions.

This differs from traditional PCR where collection of data is only at the end-point, or plateau, of the reaction. The assay can accurately detect more than 90 known species of mycoplasma, related species Acholeplasma laidlawii and Spiroplasma citri, and other species listed in corresponding pharmacopoeia so.

Overall results are ready within hours, offering a same-day detection assay that allows testing of in-process samples during manufacturing. If a positive result is obtained, the user can proceed to identify the exact mycoplasma species present in the sample using microbial identification systems. By detecting and identifying the contamination at the molecular level at the earliest possible, the opportunity for timely action and likelihood of preventing the compromise of downstream processes is increased.

Detection Enhancement

Rapid molecular technologies offer improvements to detection and identification of contamination in both traditional pharmaceutical and newer biopharmaceutical manufacturing facilities, leading to better product safety and quality.

Stringent controls are in place at every stage of pharmaceutical production. (Source: Applied Biosystems, a division of Life Technologies)

Finished batch of biopharmaceutical products. It is essential that pharmaceutical products are safe and of high quality, to minimize overall product risk. (Source: Applied Biosystems, a division of Life Technologies)

These methods can help pharmaceutical companies increase productivity and reduce risks, with time-to-result being cut down from days to just a few hours. Costs can also be reduced, while giving manufacturers greater control through in-house testing.

The methods can also find a niche in related applications and may be ideal for public health laboratories, cosmetics and personal care product manufacturing, food-testing laboratories and academic and research centers.

These rapid molecular methods look likely to experience greater popularity in future, as they help ensure timely intervention to preserve a company's investment in bringing products to market. **PA**

Product Lifecycle Management: Investing in Efficiency

Christopher Holmes
Vice President
Manufacturing Insights Asia Pacific
(an IDC Company)

PLM provides the tools for lowering costs, increasing revenue and reducing time-to-market for new products.

With the current economic uncertainty hanging over the manufacturing industry, many companies are reconsidering their strategies. Companies are paying more attention to process improvement initiatives to remove waste, drive down costs, and differentiate themselves from competition. Recent research suggests that investment in Product Lifecycle Management (PLM) applications will see a high level of interest in the coming two years.

Integrated Support

PLM in manufacturing, involves a suite of IT applications integrated to support activities to develop, model, track and manage products.

It also used to manufacture, sell, maintain, and, finally, to retire these products. The typical functionality that is found in PLM applications is engineering software, including mechanical computer-aided design, engineering, and manufacturing (MCAD/CAE/CAM); as well as product information management.

Other features include enterprise asset management software for maintenance, repair, and overhaul to track product quality and perform failure analyses. Project and portfolio management software is used for new product development and introduction (NPDI).

In addition, a comprehensive solution should also comprise of collaboration applications, not only for team collaboration within the enterprise but also with external business partners. Another aspect would be business performance measurement software for analyzing cost efficiencies and searching for process improvements.

The program should bring together a variety of detailed product information from the different applications within the organization. These include accounting, human resource information and manufacturing resource planning. Other examples would involve logistics applications such as transportation planning and management, warehousing, as well as return logistics, retail and wholesale distribution operations management software.

Process Improvement

This also means that the adoption of product lifecycle management tools impact the entire organization. The majority of functional process owners ranging from engineering to manufacturing and supply chain, are involved in the decision making process and implementation of the PLM applications.

The key driver for the adoption of PLM across all industries is productivity improvement. When we look at other drivers, the need to reduce product related costs ranks second, while the need to improve quality comes third. It is interesting to note that innovation is not highly rated.

However, when looking at the results from the perspective of the value chain, a different picture is formed. More often, value chain models are used to reflect various organizational functions and the

Drug Manufacturing

Making a Comparison

A major difference across the value chains is in cost reduction. Lowering product-related costs is a top priority for brand-oriented companies that operate with narrow margins. Engineering-oriented value chains that have mature lean practices still rate cost reduction high, relative to other initiatives, but yet lower than the other value chain companies.

Another noticeable difference is in the ranking of quality improvement goals. Improving quality is a top priority for engineering-oriented companies. The automotive, farm, construction, and industrial machinery industries have been known for spending 2-3% of product revenue to honor warranty obligations and for massive recalls – a direct outcome of adverse quality.

Brand-oriented value chain (BOVCs) companies ranked quality improvement the lowest priority compared to other value chains and low, relative to other business improvement goals. This does not mean that these companies are unconcerned about product quality. Most of them, like food and pharmaceuticals, are highly regulated, whereby the quality of products and the consistency of manufacturing processes have reached a level of maturity that is no longer considered a goal, but rather a standard.

BOVC product companies lead the other value chains in pursuing new markets. These companies need to be highly innovative and excel in creating new product variants for increasingly narrower markets.

A program that supports PLM should involve logistics applications such as transportation planning and management, warehousing, as well as return logistics. (Source: Alfonso Romero, US)

interrelations between the primary and supporting activities to achieve a business goal.

While this view has been quite popular, most manufacturers today are part of different sub-vertical supply chains, eg, a manufacturer supplies to both electronics and automotive customers, each having a unique set of challenges, coupled with the complexity of managing entities across multiple geographic locations.

The traditional value chain model therefore needs to be mapped onto the various supply chain processes, in order to get a better understanding of the common challenges, and strategies needed to address them. Value chain mapping by key manufacturing processes provides a different perspective to analyze business processes and understand fundamental issues. The four types of key value chains are:

- Engineering-oriented value chains (EVOCs): These are characterized by segments that are driven by complex products such as in automotive, aerospace, industrial machinery, farm/construction equipment, medical equipment, consumer durables and transportation equipment.
- Technology-oriented value chains (TOVCs): These have a physical flow of goods that are dictated by the iterating cycles of key underlying technology (eg, processors) and include segments such as semiconductors, electronic manufacturing services (EMS), high-tech equipment, and consumer electronics.
- Asset-oriented value chains (AOVCs): These are characterized by investments in property, plant, and equipment. They include segments such as chemicals, pulp/paper, metals, and construction materials.
- Brand-oriented value chains (BOVCs): These are characterized by branded products that serve consumer markets. BOVCs include segments such as health and beauty, food and beverage, and apparel.

Investment Considerations

Larger pharmaceutical manufacturers fall into the category of AOVCs and are characterized by investments in property, plant, and equipment and include segments such as chemicals, pulp/paper, metals, and construction materials.

Research has shown that AOVCs traditionally do not invest heavily in PLM tools (Global PLM Study, October 2008). Computer Aided Design (CAD) investments have focused on plant architectural drawings. Product data management has been centered on formula creation, connected to investments in manufacturing execution and enterprise resource planning (ERP) applications.

With a relatively small sample size, absolute conclusions cannot be drawn but the indications are that PLM strategy and process improvements are derived from the key business objective – increasing revenue.

First area of investment is directed towards improving manufacturing yields and supply chain processes. The second is on shortening time-to-market for new products, leading to faster product development times. IT investment is centered on supply chain applications and connects the various levels of the supply chain.

PLM is likely to see the next big round of investments similar to ERP application investments a few years ago. As it comprises a suite of applications, organizations will implement different applications at different times, with each one having its own specific process and application roadmap.

Given the current economic uncertainties, the initial adoption of process improvement tools looks likely to be predominantly driven by the need for cost reduction and overall process efficiency. **PA**

QC Systems: Getting it Right

Jo Smewing
Applications Manager
Stable Micro Systems

Quality control mechanisms are necessary for ensuring product integrity – and consumer safety.

The pharmaceuticals industry is one of the most tightly regulated industries across the globe. According to *Chemistry World*, December 2007, estimations of the cost of taking a drug to market sit at the $1 billion mark – with much of this spending being pumped into lengthy trials and rigorous analytical tests. Proving the efficacy, quality and safety of a pharmaceutical product to gain confidence and approval for the market is a significant investment. But what of the product after it is approved? Does investment in quality evaluation stop here?

With the center of gravity for the pharmaceutical industry shifting from the US and Europe to Asia Pacific, this region is seeing both multinational and local pharmaceutical companies acquiring international market share. Manufacturers who want a part of this success need to stay ahead. While the development of a new product requires extensive analysis and control, the process of distributing it to the wider market throws up a whole different set of challenges.

Safety in Numbers

One of the most challenging aspects of pharmaceutical manufacturing and distribution is achieving handling and storage stability. Producing a single unit of a product to the required quality specification is one thing, but packaging and transporting it, with hundreds of thousands of others, is a different matter.

Weaknesses in structure or formulation can present product failure risks at various stages of the distribution process. Pharmaceutical manufacturers need to ensure that products are robust enough to withstand packing procedures, storage and transit conditions, as well as consumer handling. The implications of product failure can be as disastrous for over-the-counter medicines as they are for prescription drugs – dissatisfied customers, disgruntled consumers, lost contracts, damaged reputation and, ultimately, reduced profits.

The industry has worked to develop and enhance quality control measures that help to predict and refine product stability. Texture analysis instruments have played a significant role. These devices offer the repeatable, scientific quantification of material robustness, the results of which can identify product weaknesses, predict, and subsequently avoid product failure.

Traditional tests have enabled the analysis of parameters such as tablet hardness, gel strength and mucoadhesion. While these tests continue to provide valuable data, texture analysis experts now have to respond to rapid innovation within the pharmaceutical industry, as new delivery and encapsulation formats are introduced. As a result, the scope and capabilities of testing instruments have widened significantly.

The capsule tensile rig measures the force required to split one half of a hard gel capsule, enabling manufacturers to investigate the effects of fillings on the mechanical strength of the capsule shell. (Source: Stable Micro Systems)

Capturing Capsule Weakness

One of the latest developments in testing is the capsule tensile rig. This instrument measures the force required to split one half of a hard gel capsule. It allows manufacturers to investigate the effects of fillings on the mechanical strength of the capsule shell. It also helps to identify changes that may impact the shell's stability and long-term performance.

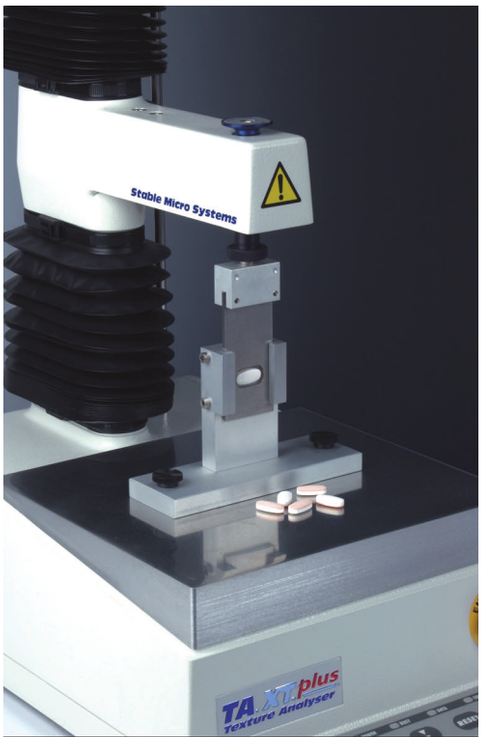
The simplified manufacturing process of hard gelatin capsules and their ability to withstand higher filling temperatures is attractive to many manufacturers. Yet, the introduction of certain types of liquids (such as hydrophilic solvents) to hard capsules can often affect the mechanical properties of the shell, causing them to become brittle or soften. If the texture of a capsule is compromised, it may not be able to withstand handling and storage, resulting in the leaking of the fillings.

Compressive tests may not be able to distinguish the anomalies adequately as the effects are likely to be progressive, displaying only minute changes initially.

The capsule tensile rig is designed to help identify subtle degradation, providing valuable information which can be used to avoid subsequent capsule failure. For example, manufacturers can identify the effects of a liquid filling on the strength and stability of capsules and therefore reformulate the liquid type or capsule accordingly.

Before testing, the filling of the capsule is removed and the empty shell is mounted to a separating rod fixture on a texture analyzer. Vertical movement of the upper rod is then applied until the capsule is split apart,

Drug Manufacturing



The bilayer tablet shear rig is used to gauge and optimize the stability of tablets which contain isolated immediate and controlled release component layers. (Source: Stable Micro Systems)

while software records the force required to do so. This test highlights three important parameters: elastic stiffness (if a linear region on the graph is present), tensile force and elongation at breakpoint. A reduction in elastic stiffness and tensile strength occurs when capsules become softer and therefore show a tendency to fail.

Cracks Under Control

The pharmaceutical industry is one of the world's biggest users of powder. Many products, such as paracetamol, are produced in powder format and then compressed into tablets. Powder compaction is an essential step in the manufacturing process and it is essential to prevent products from cracking during processing. Their liability to failure is influenced by the powder's processing properties, such as density variations introduced during die filling and/or compaction.

The characteristics of powder in its bulk form can enable manufacturers to predict its behavior when compressed. However, the need for more a targeted analysis of powder compaction has been identified and, as a result, the powder compaction rig was developed.

Available in high or low tolerance variants, the rig accurately measures the force and/or punch displacement required to compress powders into tablets. Using software, the powder compaction rig produces precise measurements that enable pharmaceutical product manufacturers to produce powder compacts with consistent porosity. It accurately assesses the force needed for the punch to travel a specified distance. It can also be used in target force mode to assess the effect of fill level on tablet thickness.

The high tolerance powder compaction rig is suited for high force applications where the punch/die clearance is critical. This fixture is auto-aligned using a universal adapter, which saves time and avoids human error. The low tolerance version is suited to other powder compaction applications, such as assessing granule friability, where punch/die clearance is less important.

Shear Strength

Sophisticated methods for powder characterization, along with analysis techniques for hardness and coating adhesion, have enabled manufacturers to obtain valuable data on the stability of standard tablet formats. However, the development of bilayer tablet formats, which contain isolated immediate and controlled release component layers, has given rise to other analytical requirements.

Such formulations are increasingly popular as they provide efficacy for consumers as well as ease of production for manufacturers. Ensuring that one tablet layer does not impact on another is instrumental to the remedial benefits of bilayer medication, and to the safety of the consumer. But isolating two release components in separate layer formations can prove complex for manufacturers.

The characteristics of each active pharmaceutical ingredient in a bilayer tablet often differ, leading to problems in tablet composition which may in turn result in cross-contamination. Common issues include layer separation, insufficient hardness and inaccurate individual layer weight control. Manufacturers need to be able to gauge the stability of the layers, to ensure the product reaches the user in its intended format.

The bilayer tablet shear rig is used to analyze the strength of bilayer tablets, allowing pharmaceutical manufacturers to identify weaknesses and improve the quality and stability of their products. The rig is attached to a texture analyzer, which analyses layer separation. The tablet sample is placed in the central cavity of a guillotine-type blade, which is then compressed until the two components of the tablet are sheared apart.

The force taken to shear the tablet, as well as the distance to failure, is calculated. The lower the force required to shear the tablet, the more likely it is that the layers will fail during manufacture, packing or consumption. Visual characterization of the fracture surface enables quantification of the percentage of each fracture failure. This is important in enabling manufacturers to optimize adhesion between the two tablet components.

The stability of a pharmaceutical product is paramount to the consumer's acceptance of it, as well as to its subsequent efficacy and safety. It is vital, therefore, that manufacturers scientifically assess potential changes in the structure or character of their products throughout processing and distribution.

Texture analysis instrumentation provides solutions that offer targeted, repeatable testing that produces actionable data. As the Asian pharmaceutical industry innovates, materials analyses needs to evolve, developing and adapting to provide instruments for emerging test requirements. **PA**

The powder compaction rig ensures that powder compacts are compressed precisely to optimize processing. (Source: Stable Micro Systems)

Information Systems: Asia On-Trial

Chris Huang
Senior Product Manager
Sparta Systems

Systems that provide accurate and timely information are required to support clinical trials in Asia.

In recent years, there have been several factors driving the shift of clinical research from the more affluent regions of the world (such as North America, Western Europe and Australia), towards the less-developed, emerging regions such as Asia, Latin America, Eastern Europe, Middle East and Africa.

Key factors include the ability to reduce operational costs and the continuing global harmonization of guidelines and practices for clinical research. Other aspects involve the rapid growth of contract research organizations (CRO) focused on emerging regions, and the ability to rapidly recruit patients from a large population of viable subjects – many of which have never participated in a clinical trial.

Countries such as China, India, and South Korea are experiencing some of the highest growth rates – as high as 47% in China annually – in clinical research sites. (Fabio Thiers, Anthony Sinskey, Ernst Bendt, Trends in the Globalization of Clinical Trials, January 2008)

Over the next 10 years, the population of China is expected to see an increase, equal to the total current population of the US. (Dr Ogilvy, Going Global, December, 2008).

Counting the Cost

As the cost of bringing new therapeutic treatments to market grows, Asia is becoming an attractive option for lowering the cost of industry-sponsored clinical trials. Some of the most common savings are found in operational costs related to facility and human resources at an outsourced CRO.

With the slowing global economy, budgets of organizations that sponsor trials are being reviewed in areas such as software tools that aid clinical research. These tools include systems for Electronic Data Capture (EDC), Clinical Data Management (CDMS), Clinical Trials Management (CTMS), Clinical Supplies Management (CSM), Clinical Quality Management (CQM), Adverse Event Reporting (Safety), Product Registration Tracking, Interactive Voice/Web Response (IVR/IWR), and Patient Related Outcomes (PRO).

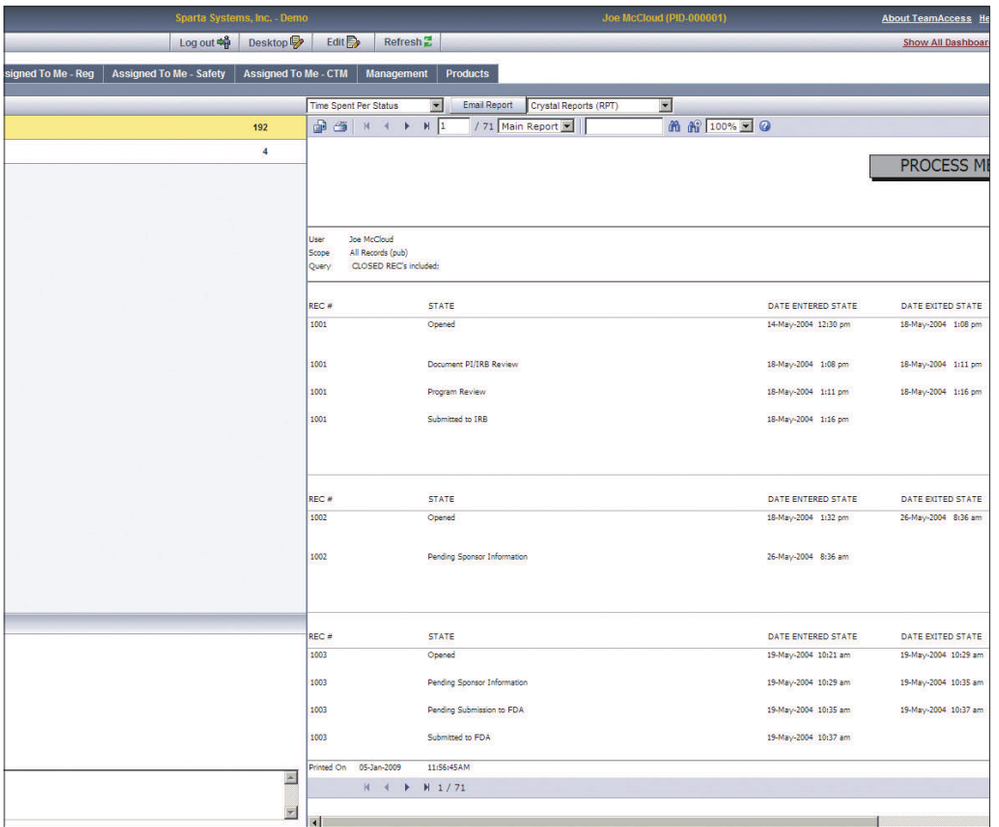
Solutions that allow organizations to maintain a low total cost of ownership are those designed with comprehensive configurabilities, as opposed to fixed architectures. This flexibility allows the solution to be adapted to meet the multiple and varying needs of the different systems within a single configurable tool.

Implementing a single system and configuring the tool for multiple and related business processes allows organizations to get the most out of their investment. It provides the ability to segment these configurations by clinical process groups and to provide global information that is shared across clinical process groups.

Such systems also need to support flexible security features to restrict a user's access to designated areas in the overall system, depending on his/her role. This allows the system to adhere to patient and data privacy regulations, such as the Health Insurance Portability and Accountability

(Source: Sparta Systems)

Clinical Trials



(Source: Sparta Systems)

Act (HIPAA) and the EU Data Privacy Directive.

Standard Compliance

The execution of clinical trials in Asia and other emerging regions is not without its inherent challenges and issues. These include: a lack of infrastructure in some regions, changing regulations, intellectual property violations, and concerns about compliance with Good Clinical Practice (GCP) standards.

Clinical systems that manage and track quality and compliance can also play an important role in the continual improvement of clinical trials. For example, a single solution that is used for Product Registrations and Tracking, CTMS, CSM and CQM, should also have built-in non-compliance and deviations handling around these business processes.

This allows for the automatic and continual monitoring of various aspects of clinical trial activities. These include the timeliness and quality of clinical supply shipments to research sites, the quality of clinical monitoring, standard metrics around data queries, timely adverse event reporting, protocol deviations, and clinical site and personnel performance.

With the quality and compliance procedures that built into a clinical solution, corrective and preventive actions as well as effectiveness checks can be easily tracked. This is to ensure the continual monitoring and improvement of clinical trials being run in emerging regions. If certain clinical sites have a propensity for protocol deviations or where there is suspicion of clinical trial data fraud, the suspect and actual root causes of these deviations can become valuable information for planning future trials.

Local vs Global

Trial sponsors can choose between a global and local CRO to run clinical trials. Most global CROs have local offices around the world including Asia, and are the choice of many US companies. There are potential benefits for using local CROs as well, such as the potential for greater expertise in local regulations, site feasibility/selection, and patient recruitment.

Regional clinical trial supply depots are commonly identified for trials that ensure the timeliness of drug supplies, kits and labeling. However, the quality of these services in Asia still remains a concern for some outsourcing companies. In such cases, the clinical systems that track the overall quality and project timeliness of the clinical trial process, can also be used to monitor the performance of partners, such as CROs and regional supply depots.

Clinical research guidelines and practices are becoming harmonized through the efforts of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This means that the execution of a clinical trial in Taiwan, Singapore, India or China is likely to share similarities with those run in North America.

A common scenario today may be a global clinical trial with sites in the US, Asia, and Europe. In such a situation, clinical research tools need to support internationalization features. They also need to be ubiquitous and easily accessible to end users, and manage the flow of information.

Internationalization features, or multi-lingual support, should provide full or partial localization of the user interface for menus, field prompts and entered data. To support global users, an ideal system must easily provide secure access through a web-based user interface without the need for a local installation by the end-user (ie, no client installation or plug-ins required).

The complex coordination of global processes requires the ability to capture, track and notify all appropriate users and affiliates of information in an immediate or timely manner. For example, a global pharmaceutical company has adopted a global safety reporting mantra that basically states "any case, anywhere, anytime." So if a clinical or spontaneous adverse event should occur in a patient located in India, it should also be reported to the respective regulatory agencies in US, Canada, Europe, Asia, and Australia.

With clinical research being outsourced and managed globally, the systems that are deployed need to support global users and capabilities.

As the overall number and percentage of clinical trials continue to increase in Asia and other emerging regions, the systems that are used for clinical research need to be flexible, adaptable and provide information in real-time. With trial sites moving into different regions in an attempt to reduce costs, there is a need for the availability of timely, quality information. Systems that track the overall trial processes can help monitor quality and reduce costs, allowing companies to get the best of both worlds. **PA**

Moving with the Times

Faced with tightening credit policies in Asia, companies need to adapt. Robert Solazzo, Marketing Manager, Pharmaceutical and Biotech, Asia Pacific, Agilent Technologies and Yukari Haramaki, Director, Market Development, Asia Pacific, Waters give their own views about what lies ahead, and how companies should respond.

Robert Solazzo
Marketing Manager
Pharmaceutical and Biotech
Asia Pacific
Agilent Technologies

Yukari Haramaki
Director, Market Development,
Asia Pacific
Waters

PharmaAsia: How are tightening credit policies affecting the purchase of drug manufacturing equipment in Asia?

Solazzo: While some companies have been adversely affected by the recent financial crisis, others have continued to invest in projects that they are committed to. Novartis has recently announced postponing their expansion into Singapore, yet Abbott and Genentech continue to invest in South East Asia.

We still see strong growth coming from South Korea despite the recent devaluation of the Korean Won and expect this expansion to continue in the year ahead. Korea has a strong domestic pharmaceuticals market, and its growing middle class is fuelling growth in pharmaceuticals, especially generics.

Haramaki: Generally speaking, Asia is well positioned, as most drug manufacturers are producing active pharmaceutical ingredients (API) or generic pharmaceuticals with equipment purchases funded through existing operating budgets. Some in the industry are of the opinion that the generics business will grow as consumers shift away from branded drugs toward generics, to offset healthcare costs.

Asia is producing more tablets today, and these tablets need to be tested for quality. So, while consumer pharmaceutical demand may be slowing, Asia's pharmaceutical manufacturing market remains viable with potential for growth.

PharmaAsia: In your view, which are the most affected countries?

Solazzo: Perhaps the most affected country in Asia has been India. The Indian pharmaceutical industry has experienced huge growth over the last five years. In the last six months, we've seen some softness in this market, as several key organizations in India have funded their growth through institutions that were directly affected by the global financial crisis.

We expect this period of downturn to be reasonably short, as India remains an attractive market driven by both domestic and foreign growth for lower cost, high quality generic pharmaceuticals. North Asia continues to perform well and we expect that to continue especially as demand for pharmaceuticals continues to grow in these regions.

Haramaki: While the tightening credit policies are taking effect throughout Asia, the customers that are able to receive funding approval are those that are able to demonstrate clear business benefits as a result of the investment.

For example, we have observed that the purchasers of analytical instruments need to demonstrate how that equipment would be able to provide critical QC testing faster, while utilizing fewer resources or improving workflow.

PharmaAsia: How are these credit policies affecting R&D spending in Asia this year?

Solazzo: While many locally based organizations have curtailed spending in the short term, other opportunities have opened up in adjacent sectors. For example, many governments have actually increased the amount of money available in the public sector in an effort to sustain growth.

This has had a positive impact on business coming from academic and government sponsored research, especially in the life sciences. In fact, many multinational pharmaceutical organizations are utilizing the expertise and infrastructure found in universities to conduct some of their R&D activities. This trend seems to be expanding as universities and state-funded research look toward enhancing relationships with the private sector.

Haramaki: Throughout the region we are hearing a similar question from our customers: 'How can we maintain or increase laboratory output with more productive, efficient and easier to use technologies?' Across Asia, laboratory productivity will be an important issue in 2009.

China, Korea and Japan represent the three largest markets for commercial pharmaceutical R&D. China's private sector, driven mostly by large multinational companies, has invested significant resources. We do not expect these organizations to be affected by current banking challenges as long as they continue to demonstrate a positive cash flow.

South Korea is in a similar situation as China, albeit on a smaller scale. However, private pharmaceutical companies in Korea have not only been hit by tightening credit, but also the depreciation of the Won and falling demand from overseas markets. These additional factors are adding pressure to R&D pipeline prioritization and spending in the country.

Japan is also experiencing significant challenges as nearly all multinational pharmaceutical R&D functions have been closed in the country. The net result is that the R&D goals in Asia are centered on the need to improve laboratory productivity with limited resources.

PharmaAsia: What challenges and opportunities are you expecting in the year ahead?

Solazzo: Like many companies, we see 2009 as a challenging year. We will continue to provide excellent support to our existing and future customers. We believe that Asia will continue to be attractive to western pharmaceutical companies, and that investments will continue to grow.

China, in particular has achieved excellent results and growth over the last 18 months and this is continuing in 2009. Agilent is involved in providing solutions for traditional Chinese medicine, biopharmaceutical and clinical analysis, so any decline in the classic western pharmaceuticals segment will likely be offset in other segments.

Moreover, many governments are providing funding and encouraging closer ties between academia and industry for basic research. This will result in further business in 2009, especially in the life sciences such as drug discovery, proteomics, metabolomics and genomics.

We expect to see greater emphasis on regulatory compliance throughout Asia as the FDA and local regulatory agencies increase their focus on quality and the enforcement of international standards. This is likely to result in companies investing in tools and infrastructure, to meet these requirements. Our company has strong core competencies in the area of regulatory compliance.

Additionally, as foreign companies look to control expenses, Asia remains an attractive region for bio/pharmaceuticals outsourcing, and we expect further opportunities as MNCs continue to invest in drug development, new lead compounds identification, conduct clinical trials and manufacturing outsourcing. We will continue to invest in growing our portfolio of solutions for our customers as well as expand our local capabilities to support them.

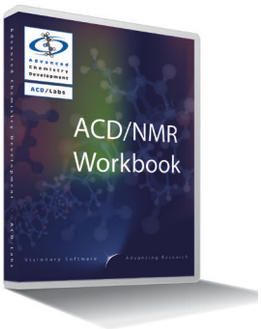
Haramaki: The biggest challenge for Waters Asia may be in ensuring that purchasers in the pharmaceutical industry continue to recognize the importance of 'working smarter', rather than choosing investment options purely based on cost. The focus should be on the business benefits that can be reaped by adopting innovative instruments.

For example, our customers' feedback indicate that their chemists are working more efficiently because more than half of their usual procedures have been eliminated by using the Acquity UPLC. This means that they are requiring fewer instruments to do the same job. This is just one example of working smarter – saving money both now and in the future.

Our focus in the year ahead, is to continue improving customers' workflow and laboratory efficiency through innovative technology.

Product Focus - Lab Equipment

ACD/NMR Workbook



The Advanced Chemistry Development/ Nuclear Magnetic Resonance (ACD/NMR) Workbook comes with features that allow the processing, analysis, and interpretation of 1D and 2D NMR spectra simultaneously.

The NMRSync technology instantly applies analysis changes made in one NMR spectrum, to all others relating to the same structure. The convenient project console allows the user to see all relevant information pertaining to the dataset. Reporting is facilitated with the Common Assignment Table.

Assigned experimental spectra, structures, tables, annotations, and other associated data can be stored in the database. Searching is performed through a variety of text, structure, and spectral searches. ACD Labs, www.acdlabs.com/nmrworkbook

PakSense Ultra Labels for Monitoring Temperature

PakSense Ultra contact labels monitor temperature and time length of a perishable item during distribution. The labels are flat, about the size of a sugar packet, and are able to digitally record the time and temperature of a product's environment. Acceptable temperature range specifications are pre-programmed into each label by the manufacturer.

Users simply snap the corner of the label to activate and attach it to their product. Lights will indicate if temperature abuse has occured and all data collected by the label can be downloaded and graphed. PakSense labels provide insight into what happens to products during distribution. DGMI, www.dmgi.com.sg

Activotec: Peptide Synthesizer

The Activo-P11 peptide synthesizer from Activotec comes with reactor heating to increase coupling efficiency for difficult or long sequences. The intuitive wizard software prompts users and enables the rapid definition of protocols. Users just need to enter the peptide sequence, fill in the quantity required, define the resin to use and then press run.

Cycle times of as low as 30 minutes per coupling are now possible and even long peptides can be synthesized. Disposable reactors and amino acid containers aid easy installation, removal and maintenance. The system is able to synthesize peptides in the 0.1 - 2.0 mmol scale. Activotec, www.activotec.com

Velocity11 Pipetting Technology

Velocity11 has designed a BioCel system configuration that addresses complex pipetting protocols needed for DNA preparation. It uses an automation system built around its VPrep high-speed precision pipetting technology.

The BioCel system comes with scheduling software, flexible liquid handling options, a high speed central robot and the ability to integrate third-party instruments. Using this system, the VWorks software and scheduler, it is possible to provide the unattended automated preparation of 200 plates in four hours. The automated process also eliminates sources of sample contamination.

The system is capable of assembling genomics reactions, dispensing samples for compound preparation or processing biological samples in screening applications. It is available in three different sizes and offered with various options for enclosures and environmental control. Velocity11, www.velocity11.com

Biomark PCR System

The BioMark Real-Time PCR System from Fluidigm Europe is designed for dynamic arrays and digital arrays. The system integrates thermal cycling and detection of polymerase chain reaction (PCR) assays. It acquires data for each reaction chamber of the IFC chip simultaneously and can operate in either end-point or real-time detection mode.

The system is supplied with data collection and data analysis software for genotyping, digital and real-time PCR. Real-time PCR analysis software displays the analyzed data in multiple formats, including color-coded maps of every reaction chamber on the IFC chip, amplification curves, and numeric tables. Intuitive software design enables even new users to manage, annotate and archive results.

Because the system is designed for proprietary licensed 5' nuclease assays, laboratories may easily switch to dynamic arrays and digital arrays for PCR while continuing to use tried and trusted reagents and protocols. The entire system, from the footprint of the chips to the architecture of analysis and database software, adheres to industry standards, ensuring integration with established workflows. Fluidigm, www.fluidigm.com

Product Focus - Lab Equipment

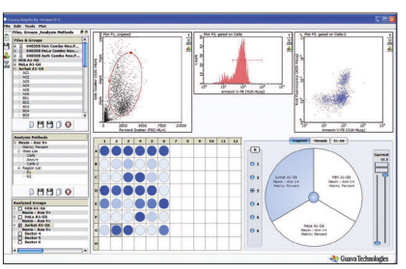
Cedex XS Cell Analyzer

The Cedex XS from Innovatis is a semi-automated, image-based cell analyzer. It is capable of delivering cell concentration using the Trypan blue exclusion method, cell morphology, cell aggregation, and growth data from sample volumes as small as 10µl. Measurement data can be obtained by the use of Cedex Smart Slides – eight-well slides that enable multiple measurements in a single analysis that can be compared and averaged with the software.

The software enables users to compare, review, store, publish and share cell data for collaborative studies, and has the ability store up to 5,000 measurements. Its operation is as simple as: power on, insert slide, deposit sample solution and begin analyses. High resolution, 0.88µm per pixel images are quickly acquired in color, as are diameter and compactness histograms and predictive statistical data.

Detectable cell concentration range is $1x10^4$ to $5x10^6$; cell diameter range is 4-180µm; and the object diameter range is 2-180µm. In addition to being easy to set up and use, Cedex XS is constructed of rugged steel and durable enough for use in a class room environment. Innovatis, www.innovatis.com

Guava Technologies: Extracting Key Data



Guava Technologies has presented information on their recent advancements that describe an experimental methodology and the Guava Simplicity Analysis software which exploit the advantages of plate based flow technology. These improvements can expedite the drug discovery process by providing a means for extracting key findings from the data sets of small interfering ribonucleic acid (siRNA) knockdown assays.

The EasyCyte Plus system, with integrated Guava Simplicity software, provides a platform for secondary target validation and compound screening. Flow cytometers overcome the limitations of inference-based measurements of transfection efficiency and protein knockdown through direct quantitiative analysis of populations at the single cell level.

The software's intuitive architecture facilitates the process of asking biological questions on multi-dimensional data sets – through visualization of user-defined parameters in the form of heat-maps. Comparative results are displayed at the experiment level rather than on an individual well/sample basis. Guava Technologies, www.guavatechnologies.com

ActiFlow: Material Flow Aid

The K-Tron Process group has introduced ActiFlow, an alternative to other forms of mechanical hopper agitation. The machine prevents bridging and rat-holing of cohesive bulk materials in stainless steel hoppers. It is a non-product contact device, consisting of a patent-pending drive system and intelligent control unit.

For difficult flowing materials, it does away with mechanical agitators with secondary motors and gearboxes, as well as the need for flexible side wall agitation devices or aeration pads.

ActiFlow simplifies the cleaning process during material change-over and reduces headroom requirements. The device is bolted to the outside of the extension hopper, above the feed screws. Together with the control unit, it continuously activates the material inside the hopper with optimized frequencies and amplitudes. Working together with the Smart Force Transducer (SFT), filtering algorithms ensure an accurate weight signal, even with the ActiFlow running. K-Tron, www.ktron.com

Genevac HT Solvent Evaporator Series

Genevac has announced the publication of a new 20-page catalogue that provides a description of its HT Solvent Evaporator Series.

Each product section comprises technical description and basic specifications, photograph of the system, available options and key feature / benefits. Further information is provided on sample holders, software and options for fast lyophilisation and specialist applications including handling highly volatile, explosive or acidic samples. Genevac, www.genevac.com

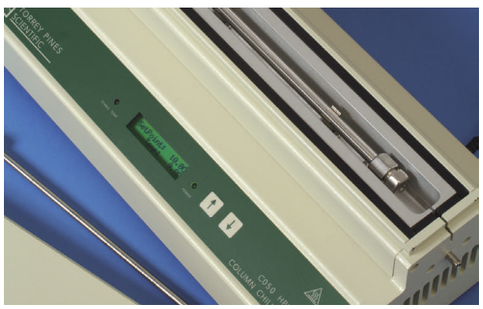
Fireboy Bunsen Burner: Safety in Use

The Fireboy Bunsen burner from Integra Biosciences is an alternative to the traditional bunsen burner connected to a laboratory gas supply. It ensures application safety by eliminating the risk of gas leaks and explosions inherent in using traditional burners.

Advanced temperature protection, flame monitor and alarm display features serve to protect both the operator and operating environment. To prevent unignited gas leakage, the burner automatically tries to reignite the flame if it accidentally extinguishes. Should it fail to do so, the unit will interrupt the gas supply.

The burner also automatically shuts off after a user-defined maximum burning time. Operating from a wide range of gas cartridges and powered from a battery, it can be used in areas of the building not served by the gas supply. With no interfering cables or tubes, the 'hands-free' Fireboy is easy-to-use. Integra Biosciences, www.fireboy.info

Product Focus - Lab Equipment



Temperature Regulation with EchoTherm

The EchoTherm high performance liquid chromatography (HPLC) Column Chiller/ Heater model CO50 from Torrey Pines Scientific, has a temperature range of 4.0°C-100.0°C. Its proportional-integral-differential (PID) temperature control software regulates temperatures to ±0.2°C.

It comes with a 5-program memory and 10 steps per program. It has the ability to repeat any program from 1 to 99 times automatically.

The unit is ideal for chiral and biomedical chromatography where below ambient temperatures help preserve bioactivity. It can be used for stabilizing column temperatures from day to day at or near-room temperatures for repeatable results.

A stable temperature indicator lamp on the front panel of the unit lights up when the target temperature is stable. Torrey Pines Scientific, www.torreypinesscientific.com

Radleys CLR

Radleys have published a technical bulletin that demonstrates how the Lara controlled laboratory reactor (CLR) is able to accurately and reproducibly control polymerization experiments.

The application note describes a series of experiments in which the CLR was used to automatically control the addition of monomer, initiator and reagent where both linear and variable rates of addition of feed materials were employed. The experiments demonstrate that the CLR can be used to automatically ensure that the molecular weight and structure of the resulting polymer can be predicted, controlled and reproduced. Radleys, www.lara-clr.com

FTS ThermoJet for Temperature Control

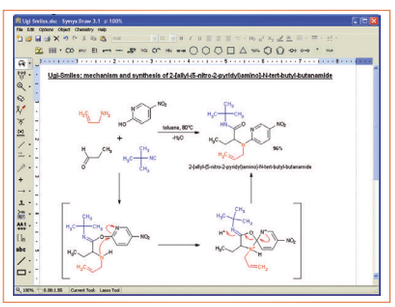
The FTS ThermoJet from SP Industries is a precision-controlled temperature forcing system designed to rapidly change the temperature of a product or device under test.

Temperature or thermal cycling is a method used to rapidly assess the reliability of products. A product which is alternately heated and cooled, causes stress to any component that has a thermal expansion mismatch. Typical applications that can benefit from rapid temperature cycling include testing of medical devices and manufactured polymer components.

The ThermoJet is capable of cycling the product under test from +230°C to -65°C, in 10 seconds. An external sensor enables precise temperature control (+/- 0.1°C).

Being compact and completely self-contained, it does not require an external cooling source such as liquid CO2 or Nitrogen. Using standard off-the-shelf environmentally friendly refrigerants, it reduces downtime and saves on maintenance costs by avoiding proprietary gases. SP Industries, www.spindustries.com

Symyx Draw 3.1



Symyx Technologies has announced that Symyx Draw 3.1, the chemical drawing application that replaces its ISIS/Draw, is available for download at no charge for academic and home use. The software enables scientists to draw and edit complex chemical structures and reactions, facilitating the collaborative searching, viewing, registering, and archiving of scientific information.

The program also offers publication-quality drawing capabilities for presentations, reports and scientific papers , as well as improved integration with the Microsoft Office suite of software applications.

Symyx Draw 3.1 is easier to use than ISIS/Draw, with its all-purpose drawing tool, multiple-undo, user-friendly toolbar functionalities, scientific symbol chooser, library of protecting group templates, and other usability enhancements. Font, color and line thickness changes can be applied with a few clicks using the formatting toolbar. Symyx Technologies, www.symyx.com

Software Package for GC/MS

Thermo Fisher Scientific has launched Lab Forms 2.5, a suite of gas chromatography mass spectrometry (GC/MS) software aimed at specific laboratory applications. It is designed for users in environmental, clinical research/forensic toxicology, food safety and general QA/QC laboratories. These software packages incorporate Method Forge, which provides an automated pathway to generating full scan methods. Wizards and templates ensure the programming of daily batches is straightforward, reducing the time required to queue samples and begin data acquisition.

Certain sample types or compound lists require intensive data review to generate the final report package. Integration, peak shapes, qualifying ion performance and quality control criteria must all be evaluated prior to releasing the results. Through Smart Reporting, data review and data reporting are dynamically linked, allowing for real-time changes to reports. Thermo Fisher, www.thermo.com/gcms

► For information on these and other related products please visit http://www.PharmaAsia.com.

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Mumbai, India
www.chemtechwe.com/pharma/index.html

Feb 23 – 25, 2009
Asia TIDES 2009
Tokyo, Japan
www.ibclifesciences.com

Mar 11 – 13, 2009
Pharma Asia
Karachi,Pakistan
www.pharmaasia.com.pk

Mar 16 – 19, 2009
BioLogistics Asia 2009
Singapore
www.terrapinn.com/2009/biolog

Mar 16 – 19, 2009
BioMedical Asia 2009
Singapore
www.terrapinn.com/2009/bma

Mar 17 – 19, 2009
Interphex 2009
New York, USA
www.interphex.com

Apr 2 – 4, 2009
PepCon 2009
Seoul, South Korea
www.bitlifesciences.com/pepcon2009

Apr 5 – 9, 2009
Biomaterials Asia 2009
Hong Kong
www.biomaterialsasia.com

Apr 7 – 10, 2009
IBC's China 2009 Pharmaceutical R&D Summit
Shanghai, China
www.ibclifesciences.com/china/overview.xml

Apr 8, 2009
DNA Day
Dalian, China
www.bitlifesciences.com/dnaday/index.html

Apr 15 – 17, 2009
Bangalore Bio
Bangalore, India
www.bangalorebio.in

Apr 28 – 30, 2009
Pharmaceutical Regulatory Affairs Asia
Singapore
www.abf-asia.com

May 12 – 14, 2009
API China
Xi'an, China
http://en.apichina.com.cn

Jun 1 – 2, 2009
Interphex Asia
Karachi, Pakistan
www.biztradeshows.com/trade-events/interphex-asia.html

Jun 1 – 3, 2009
Drug Discovery & Development of Innovative Therapeutics Japan 2009
Tokyo, Japan
www.the-infoshop.com/conference/drugdisc-japan09

Jun 1 – 3, 2009
Biotech China
Shanghai, China
www.biotech-china.com/en/index.asp

Jun 8 – 11, 2009
World Vaccine Congress Asia 2009
Singapore
www.terrapinn.com/2009/wvcasia

Jun 22 – 24, 2009
World Congress of Cancer
Beijing, China
www.bitlifesciences.com/cancer2009

Jun 26 – 28, 2009
New Drugs China
Tianjin, China
www.en.newdrugschina.com

Jul 1 – 3, 2009
Interphex Japan 2009
Tokyo, Japan
www.interphex.jp

Jul 1 – 3, 2009
International Bio Forum & Bio Expo Japan
Tokyo, Japan
www.bio-expo.jp/english

July 18 – 25, 2009
World Summit of Antivirals
Beijing & Xi'an, China
www.bitlifesciences.com/wsa2009

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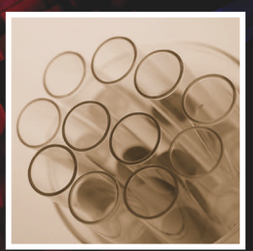

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