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Personalized Medicine for Cancer Treatment

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September 2009

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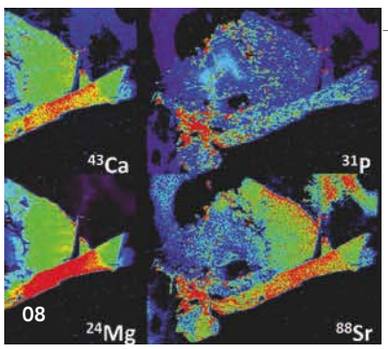

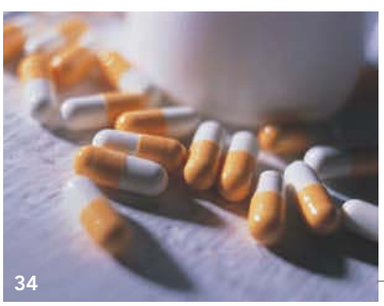

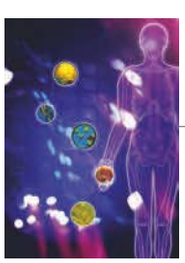

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Editor's Note

Michael Tham
Editor

The Need for Speed

In Asia's fast-growing market in pharmaceutical R&D, companies seem to be increasingly needing efficient supply chain solutions to move temperature-sensitive products. In response, express service providers in the likes of DHL, TNT and DB Schenker – to name a few – have developed cold-chain strategies to supply these needs – on time and on target.

Yet, the effectiveness of a supply chain goes beyond just technological considerations. An extensive transport network and compliance to country-specific import laws are also necessary elements that need to be addressed.

It appears that some countries have also begun to appreciate the need for speed. China for one, has implemented its Express Customs Clearance on a trial basis for Sundia MediTech, located in the Zhangjiang Hi-Tech Park in Shanghai. This has reduced the customs clearance time for the company's Contract Research Organization (CRO) shipments from three days to one.

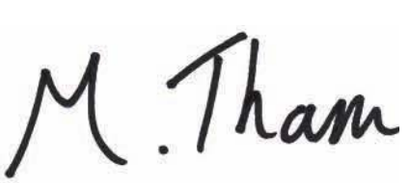
Delivering on time is a formula that also requires another active ingredient –reliability. Ortho Clinical Diagnostics has launched a remote monitoring center. The 24-7 facility continuously tracks the status of laboratory instrument performance in the in vitro diagnostic industry.

This aids customers in identifying specific service needs – by detecting and predicting potential instrument problems before the latter interrupt the ability of the laboratory to deliver quality test results.

On another front, Symyx has recognized the power of speedy information accessibility. Its ChemMobi App gives scientists the ability to view over 30 million chemical structures, properties, suppliers and other data from their iPhone or iPod touch.

Similarly, Novozymes Biopharma has recently unveiled its website that offers a wealth of information about solutions to optimize biopharmaceutical manufacturing and improve drug products.

In the fast-paced and mostly competitive world that we live in, the ability to deliver quality, reliability, and useful products plays a vital role in ensuring the survival of the fittest. Beyond this, speed is of the essence. **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
Marketing Executive
Laura Low, (65) 6780 4302; laura.low@rbi-asia.com
Ad Admin Executive
Cyndi Yap, (65) 6780 4816; cyndi.yap@rbi-asia.com

DESIGN & PRODUCTION
Design Manager
Honess Ho, (65) 6780 4333; honess.ho@rbi-asia.com
Graphic Designer
Mario Omega Ciputra, marioomega.ciputra@rbi-asia.com
Web Designer
Cindy Chen, (65) 6780 4522; cindy.chen@rbi-asia.com
Production Manager
Pauline Goh, (65) 6780 4504; pauline.goh@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

FINANCE
Senior Finance Manager
Joycelyn Ng, (65) 6780 4513; joycelyn.ng@rbi-asia.com

Managing Director, Reed Business Information Asia
Luke Rattigan, (65) 6789 9900; luke.rattigan@rbi-asia.com

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REED BUSINESS INFORMATION ASIA
The Signature, 51 Changi Business Park Central 2,
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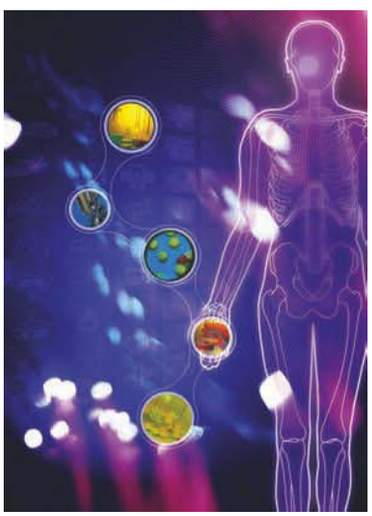
Global News

Nycomed to Acquire Local Portfolio from Sanofi-Aventis and Zentiva



Nycomed has agreed with Sanofi-Aventis and Zentiva to purchase 20 branded generic products in several Central and Eastern European countries. The agreement will strengthen the former's market position especially in the Czech Republic and Slovakia.

The transaction received approvals from the European Commission and the Czech Antimonopoly Office, and it is expected to be closed in September 2009.

In an asset transfer transaction, Nycomed will purchase a portfolio of branded generic products in the Czech Republic, Slovakia, Romania, Hungary, Estonia, and Bulgaria, with a total annual turnover of approximately €17 million (US$24 million). The company will also assume production in the coming years. Both parties agreed not to disclose further details on the transaction.

Among the acquired products is Zentiva's hypnotic Hypnogen (Zolpidem) brand in the Czech Republic, Slovak Republic and Estonia.

In the Czech Republic, the acquisition comprises a franchise of beta-blockers (Vasocardin, Betaxa, and Tenoloc), which will strengthen Nycomed's established cardiovascular business around Ebrantil (Urapidil). Among the other acquired products in this country are brands like Trental, Flavobion, and Ercefuryl. **PA**

Immunovative Therapies Announces Clinical Trials for Cancer Treatment

Immunovative Therapies (ITL) has announced that the phase I/II clinical trials of its experimental CryoStim cancer vaccine product for the treatment of advanced metastatic solid tumors will begin in September, 2009.

"Current therapies are not capable of eliminating every last cancer cell in the body and tumor recurrence is a common problem. If our experimental therapy is successful it would be possible to not only eliminate every tumor cell, but also for the immune system to remember the tumor in order to prevent recurrence," says Michael Har-Noy, CEO and chief technical officer.

CryoStim is an individualized cancer vaccine that is made inside the body by combining the experimental AlloStim drug with the killing of a selected tumor by the minimally invasive procedure called cryoablation.

AlloStim contains living immune cells attached to microbeads that are designed to stimulate and direct the human immune system to directly kill cancer cells wherever they reside in the body. The trials will be conducted at the company's clinical research subsidiary in Carlsbad, California. **PA**

Sandoz Launches First Generic Version of Prograf Capsules

Sandoz has introduced tacrolimus capsules, a generic equivalent of Prograf, in the US. Tacrolimus is an immunosuppressive treatment that is used to prevent the rejection of a kidney or liver transplant.

According to IMS Health, Prograf had US sales of US$929 million for the 12 months through April 2009. The company will market tacrolimus in capsules of 0.5, 1 and 5 mg strengths. **PA**

Integra Biosciences and Viaflo Team Up

Integra Biosciences and Viaflo Corporation have signed agreements to combine the two companies under the name of Integra Viaflo Holding. The group will be active across world markets under the brand Integra.

The former will receive direct access to the US market through the Viaflo sales network. The former also receives access to a complete line of handheld pipetting systems and associated plastic disposables.

Viaflo will receive representation and access to European and global markets through the former and its network of specialist distributors. **PA**

Market Report: Authorized Generics Agreements

As pay-for-delay agreements look to be on the way out of the pharmaceutical industry in Europe and the US, a report by Datamonitor forecasts that the number of Authorized Generics (AG) agreements will grow – in tandem with the increasing convergence between branded and generics companies.

Competitive pressures in the US and Europe have altered the brand-generic dynamic, to the extent that the line between the two is beginning to blur, with AG agreements being one outcome of these developments.

The growing trend for branded companies – notably GlaxoSmithKline, Sanofi-Aventis, and Pfizer, to bolster their generics presence also means that the strategy of fielding own-generics will gain traction.

Authorized generic agreements, the strategy by which branded companies market generic versions of their own branded drugs, provide innovators with a means of capitalizing upon the generic erosion of their own brands, thereby maximizing revenue streams from a mature product.

Authorized generics are therefore something of a late-stage drug lifecycle management strategy for branded pharma. The generics industry is more divided on the issue. For those companies with the means to aggressively challenge patents and get to market early, AGs are a considerable irritant. However, for smaller players these agreements represent a valuable competitive advantage, especially in the US than in Europe.

Due to their sale during the 180-day period of market exclusivity that is awarded to first-to-file generics companies in the US, AGs are considerably more potent in the American market. The increasing use of AGs as a "bargaining chip" in reverse payment agreements in the US (but not in Europe) underlines their greater impact.

There have been calls from some in the generics industry in the US for the so-called 'Hatch-Waxman loop-hole' to be closed to prevent AG sale during the 180-day market exclusivity period, says Datamonitor healthcare strategy analyst Pam Narang. "Detractors insist that AG sale at this time is anticompetitive and a deterrent to early generics entry. However, given the accelerated price erosion that characterizes AG sale during the 180-days of market exclusivity, an outright ban is unlikely in the short-term," she says.

All AG agreements involve a branded drug and generics partner. In the event that the branded company has a generics subsidiary, the identity of the generics partner is often a foregone conclusion. Such "own-AGs" allow the branded company to retain all revenues derived from AG sales rather than just a fraction, as is the case when the generics partner is external. Therefore, own-AGs represent the best-case scenario for branded companies that are looking to market an AG, Narang says.

Datamonitor analyzed 40 AG launches that occurred in the US between 2004 and 2008. Although only a third of the 14 branded companies under investigation had the opportunity to market an own-AG, these constituted 45 percent of all AG launches. Moreover, not only was Pfizer the most frequent branded partner involved in own-AG launches, but the company was also the most common branded partner in all AG agreements analyzed, involved in 30 percent of all AG launches.

Authorized generic launches for branded drugs belonging to the Cardiovascular (CVD), Infectious Disease (ID), and Central Nervous System (CNS) disorder classes were collectively responsible for most (60 percent) of the AG launches under analysis. These three therapy areas represent the top three classes in terms of pre-generic quarterly sales in the US, totaling US$6 billion in all. This supports the idea that companies will defend their most lucrative brands – the blockbusters – with the greatest vigor, with the AG launch forming a part of this arsenal.

The average peak AG market share for these three disease classes ranged from 43 percent for CNS brands to 50 percent for ID brands. While AGs for CVD and ID brands lost considerable market share in the two years post-launch, those for CNS drugs dropped just one percent on average.

The relative stability of CNS AG market share is due to the limited number of generic competitors entering the market for a number of brands within this group, Narang says. "Indeed the extent to which an AG is able to capture and retain generic market share is often correlated with the number of bone fide generic entrants with which it must compete."

It was found that the highest value brands were associated with the greatest number of generic entrants following loss of patent protection. Brands with sales in excess of US$600 million in the quarter prior to generic entry experienced an average of 14 and 19 competitors at one and two years post generics launch, respectively (not including the AG). It is therefore unsurprising that the average proportion of the generics market captured by AGs for this group of drugs was one of the lowest observed, at only 36 percent, when products were grouped by value.

A slowdown in the number of new drugs reaching the market coupled to delays to generics entry, has spurred regulators in both Europe and the US to look more closely at the way pharma does business. While the Federal Trade Commission (FTC) has ramped up efforts to police pay for delay deals more vigorously in the US, the European Commission's long awaited antitrust report also highlights potential collusion between branded and generics companies. **PA**

S-Evans Biosciences Signs License for Menstrual Stem Cell Technology in China

Cryo-Cell International has signed an exclusive license agreement with S-Evans Biosciences (SEB), a privately-held stem cell and genomics technology company located near Shanghai in Hangzhou, Zhejiang Province, China. The partnership will allow the latter to market and manufacture proprietary C'elle menstrual stem cell technology including the processing and storage of menstrual stem cells (MenSCs) exclusively throughout mainland China.

It will also allow SEB to conduct scientific research studies using the technology to identify future potential therapeutic applications for a possible range of diseases. The license agreement will provide Cryo-Cell with future royalty fees from the processing and annual storage of menstrual stem cells.

In recent years, China has significantly increased its efforts in the field of stem cell research and practice. Currently, scientific research in the country primarily utilizes bone marrow and embryonic stem cells. Clinical applications of stem cells to treat conditions such as acute heart failure, acute liver failure and lower limb ischemia have been reported by many hospitals. A developing country with the largest population in the world, China's estimated total population is 1.3 billion of which women account for about half.

SEB believes that the future market opportunity for the C'elle service in China is potentially significant. "Stem cell research and development is well-recognized and fast-emerging in China. Our company believes that the proprietary technology of C'elle may provide women with the opportunity to collect and cryopreserve their own stem cells that have demonstrated considerable potential to be used in future therapies, and that are easily harvested from a non-controversial source," stated Dr Charlie Xiang, CEO. **PA**

IMBcom and Prolor Biotech Sign Non-Exclusive Technology License

The University of Queensland's (UQ) company for commercializing technology from the Institute for Molecular Bioscience (IMB) – has announced that Prolor Biotech has taken out a non-exclusive license to UQ's human growth hormone receptor cell line.

Current manufacturers of human growth hormone assay for potency by using hypophysectomised rodents (rats that have had their pituitary glands surgically removed). Human growth hormone is then administered to the animals and the potency is determined by measuring the animals' weight gain and length of femur.

The UQ cell line, which can measure potency or the presence of neutralizing antibodies in serum, can allow cost savings. It can also provide more reliable, consistent results and does not require animals for testing.

Shai Novik, president of Prolor Biotech said, "We believe that UQ's cell line will help us to expedite the development and manufacturing of our long-acting version of human growth hormone (hGH) – not only can the cell line measure the hormone's potency but it can also be used to detect neutralizing antibodies that are directed against hGH." **PA**

Granules India: Manufacture and Supply of Material Finished Dosage

Granules India has announced the signing of a material finished dosage manufacturing and supply agreement with a multinational pharmaceutical company.

The multi-year agreement targets the purchase of in excess of 1.5 billion doses on an annualized basis. This annualized demand represents more than 25 percent of the company's finished dosage capacity.

Krishna Prasad, MD, stated, "We are excited to take this next step forward as it validates our vertically-integrated model. This commitment will enable our finished dosage plant to ramp up production and should substantially add to our top and bottom-line figures." **PA**

Acoris and c-LEcta Form Strategic Partnership

Acoris Research, a wholly owned subsidiary of Hikal, and c-LEcta, a Germany-based industrial biotech company have entered into a strategic partnership to develop synthetic routes for chiral compounds.

The partnership combines the expertise of the former in process development and small scale manufacturing, and the biocatalysis technologies of the latter. **PA**

Sun Pharma Announces Approval for Generic Drugs

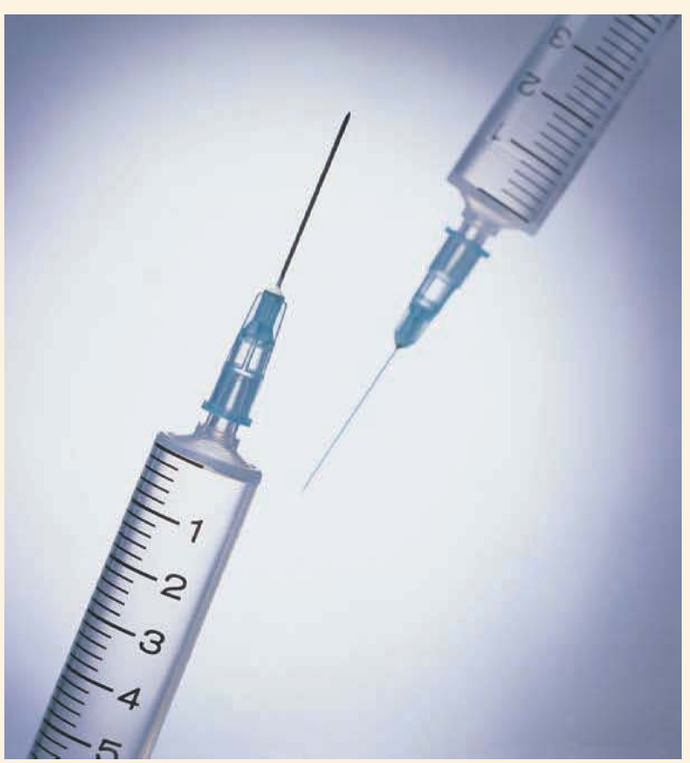
Sun Pharmaceutical Industries has announced that the US Food and Drug Administration (FDA) has granted approvals for two Abbreviated New Drug Applications (ANDAs) – the generic version of Eloxatin, oxaliplatin for injection and the generic version of Imtrex, sumatriptan succinate tablets.

Sun Pharma shares 180 days exclusivity for generic version of Eloxatin.

These oxaliplatin injections, 50 mg and 100 mg packed in single use vials, are therapeutically equivalent to Eloxatin injections from Sanofi-Aventis.

Oxaliplatin injections have annual sales of approximately US$2.3 billion in the US. The drug is used in the treatment of colon and rectal cancer.

The sumatriptan succinate tablets, 25 mg (base), 50 mg (base) and 100 mg (base) are therapeutically equivalent to Imitrex tablets from GlaxoSmithkline. These tablets are indicated for the acute treatment of migraine attacks with or without aura in adults. **PA**



Cover Story

Imaging Technology: Aiding in Disease Detection

Elemental Bio-Imaging (EBI) offers a means of accurately identifying trace metals that are responsible for neurological disorders.

Dominic Hare,
David Bishop,
Christine Austin,
Philip Doble,
University of Technology Sydney

It is currently thought that around one-third of all proteins in the human body contain at least one metal ion. It is well-established that their biological activity is dependent on the presence of this metal. These ions can act as structural features or active sites for catalysis. Trace metals are so important to cell function that cell chemistry must be characterized not only by its characteristic genome and proteome, but also by the distribution of the metals and metalloids among different biomolecules – the "metallome."

Trace metals have long had an association with many neurological disorders, with most attention being directed to the ill effects of exogenous metals rather than essential elements. Parkinson's disease (PD) is a degenerative neurological disorder that is caused by the loss of dopaminergic cells within the pars compacta region of the substantia nigra.

Coincidental with the appearance of symptoms of the disease, an elevation of iron has been observed within the substantia nigra. Iron is suspected to be involved in the formation of reactive oxygen species within the substantia nigra, which is hypothesized to lead to the death of dopamine producing cells. It is unclear if the increased oxidative stress caused by Fe in PD is a cause or effect of the disorder.

Increased brain metal levels have also been associated with normal aging and Alzheimer's Disease (AD). Copper and iron levels both show marked increases with age and may adversely interact with the amyloid-beta peptide. This causes its aggregation and the production of neurotoxic hydrogen peroxide (H_2O_2), contributing to the pathogenesis of AD. Amyloid Precursor Protein (APP) possesses copper/zinc binding sites in its amino-terminal domain and in the amyloid beta domain.

Given that trace elements are critical for cell function and are associated with neurological disorders, it is desirable to gain knowledge about the former's distribution in soft tissue. Traditional staining methods have disadvantages, in that they are often not sensitive enough, or that the stains themselves introduce impurities. Although these methods are element specific, they are not capable of measuring multiple elements simultaneously, and often detect only certain species/oxidation states of the element of interest.

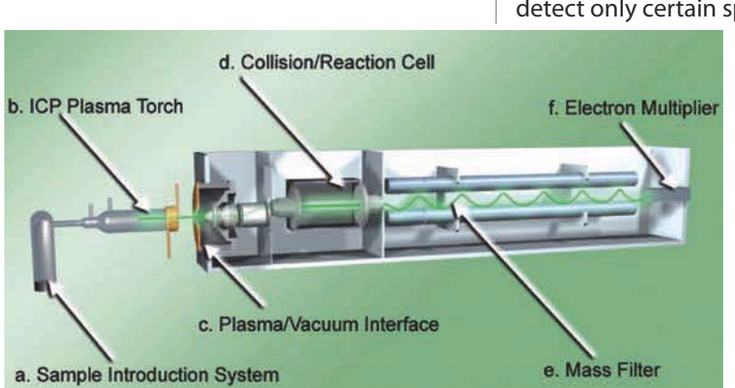


Figure 1: Inductively Coupled Plasma Mass Spectrometer. (Source: University of Technology Sydney)

Inductively Coupled Plasma Mass Spectrometry

Mass Spectrometry (MS) methods are some of the most amenable to effective trace element detection in tissue. Inductively Coupled Plasma Mass Spectrometry (ICP-MS) has isotope specificity, versatility (virtually any element can be detected), high sensitivity, linear dynamic range (105 to 106) and non-dependence on the biological species of the trace element. This makes it an ideal tool for the detection of such elements in tissue samples.

ICP-MS has long been used for trace element analysis in environmental, semiconductor and geochemical applications. Samples are introduced into an argon plasma at a temperature range between 7500K -10,000K, resulting in decomposition and ionization (Figure 1).

The ions are extracted from the plasma through an interface (c) and focused by electrostatic lenses into a Collision/Reaction Cell (CRC). The CRC eliminates residual polyatomic ions that can interfere with masses of interest, ensuring that only elemental ions remain (d). From the CRC, the ions enter the mass filter (e) which separates them by mass to charge (m/z). This mass filter is most often a quadrupole, but magnetic sector and time-of-flight analyzers are also used in some ICP-MS. Ions leaving the quadrupole strike the electron multiplier (f) that detects and amplifies the signal.

ICP-MS can be used as a detector for separation techniques such as liquid chromatography or capillary electrophoresis, and these hyphenated systems have been applied in recent years to the study of trace elements in biological samples. While such approaches have yielded valuable proteomics information, they are not amenable to accurately determining the spatial location of trace elements *in situ* in biological tissue. Current methods for this application include high-resolution x-ray spectroscopy such as the X-ray Absorption Near Edge Structure (XANES) technique, and X-Ray Fluorescence (XRF).

While these methods can detect as little as 0.1 pg and have a spatial resolution of five microns, a powerful synchrotron microbeam is required to generate X-rays of sufficient intensity to achieve this performance. As a result, the accurate spatial assessment of trace elements in tissue has been out of the reach of most laboratories until recently.

Elemental Bio-Imaging

An Elemental Bio-Imaging (EBI) system has been developed that interfaces a Laser Ablation (LA) station with the ICP-MS to provide virtual images of trace elements in tissue slices. A laser is rastered across a sample one line at a time, ablating tissue from the surface in 4 to 100 micron sections (Figure 2).

The ablated material is then swept into the ICP-MS, where the former's elemental composition is determined. In this way, an image can be built up by multiple raster lines, much in the same way that a dot matrix printer prints an image. The images are processed and displayed as color maps, with high concentrations usually designated in red and low concentrations in blue. Since the ICP-MS is a multi-element analyzer, it is possible to build maps for many elements simultaneously.

LA-ICP-MS is a more cost effective approach to trace element imaging in tissue than the current x-ray-based techniques. It eliminates much of the sample preparation associated with more traditional techniques of excising, grinding and extracting trace elements from the tissue before analysis. While this application of existing technologies is still in development, it holds the promise of providing rapid analysis times, with little operator input or expertise required.

Monitoring Disease Progression

This approach to the spatial imaging of trace elements has already been used to gain insight into the aetiology of some diseases. Elemental bio-imaging has been used to monitor the changes that occur in brain tissue during the induction of Parkinson's disease in a mouse model system. Parkinson's is caused by the loss of pigmented dopaminergic neurons in the substantia nigra, a portion of the midbrain, and is characterized by the reduced production of dopamine.

The cause of this cell death is still unknown, but there are suggestions that it may be due to an active toxic process involving oxidative stress that may be facilitated by an interaction between iron and dopamine in the Substantia Nigra (SN) region of the brain. The substantia nigra is normally rich in iron, and a further accumulation of iron has been observed in Parkinson's disease, as well as animal models of the disease.

Parkinson's disease can be induced in the rodent brain via the injection of the neurotoxin 6-hydroxy-dopamine (6-OHDA) into SN (10), in this case into one hemisphere only. Elemental

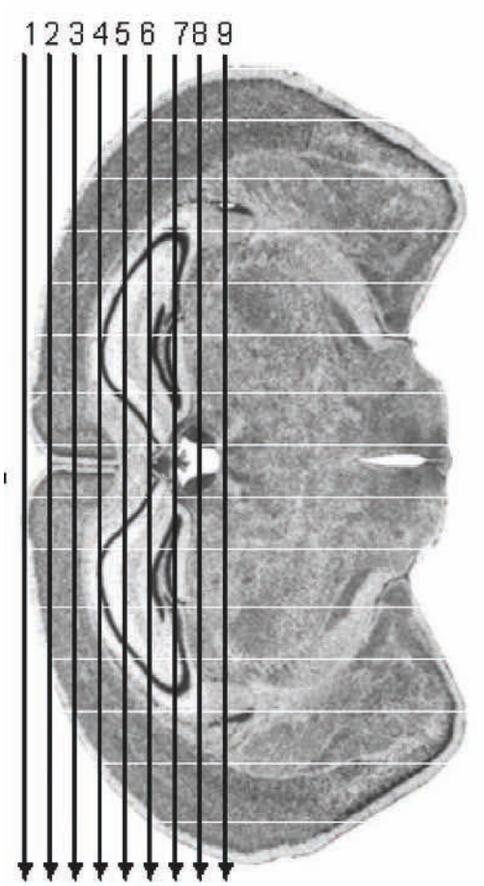


Figure 2: Image Construction. (Source: University of Technology Sydney)

Cover Story

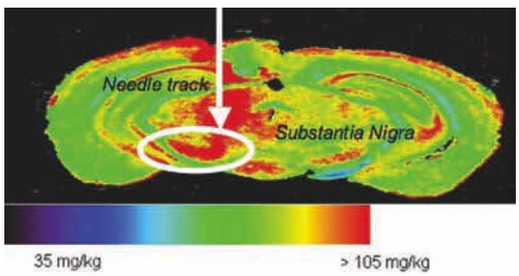


Figure 3: Imaging of iron (56Fe) in a rat brain tissue section, following the injection of 6-OHDA to induce Parkinsonism. The arrow indicates the path of the needle at the injection site, and the circled area is the substantia nigra, which is damaged in Parkinson's disease. Relative levels of iron are denoted by the color scale. (Source: University of Technology Sydney)

bio-imaging of tissue slices after the injection reveals increased iron levels both at the injection site and in the substantia nigra, versus the un-lesioned hemisphere (Figure 3).

The accumulation of iron at the injection site could be due to blood entering the injection tract and the persistence of haemoproteins. Other trace metals such as manganese, copper and zinc do not show any significant changes in distribution after injection (data not shown). This accumulation of iron in the substantia nigra is of interest as a therapeutic target, as it may be the causal component of the death of substantia nigra neurons.

The potential utility of LA-ICP-MS as a tool for the detection of calcium pyrophosphate dihydrate (CPPD) and basic calcium phosphates (BCP) in rheumatology has also been investigated. The concurrence of BCP (hydroxyapatite, octacalcium phosphate, tricalcium phosphate) and CPPD crystals and degenerative joint disease has been well established.

Although there is ample data to support the role of BCP crystals in cartilage degeneration, it is still unclear whether other calcium-containing crystals play a direct driving role in disease conception and progression, or are merely markers of joint damage.

Knee cartilage sections from a patient with osteoarthritis were obtained. The elemental distribution maps of calcium, phosphorus, magnesium and strontium are presented in Figure 4.

The corresponding regions of relatively high calcium and phosphorus intensities in the cartilage may be representative of calcium phosphate-based crystal deposits. A high frequency of CPPD crystals in articular tissue removed from osteoarthritis hips and knees has been reported in the literature. Other elements including copper, iron, and selenium did not follow the same trend in distribution.

While the virtual images of trace elements can reveal a wealth of information about changes in tissue, they must also be quantitative in order to be ultimately useful. A quantification method that is based on spin coated calibration standards has been developed.

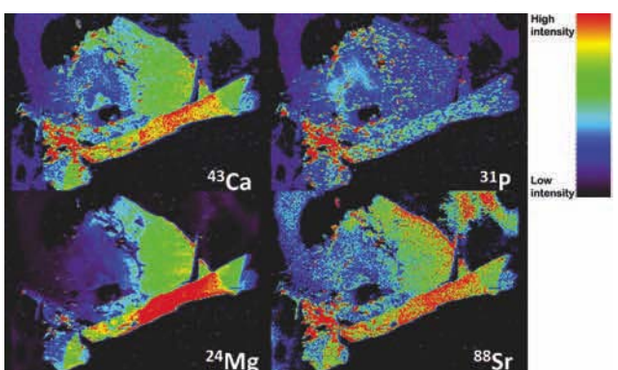


Figure 4: Elemental distribution maps of calcium (43Ca), phosphorus (31P), magnesium (24Mg), strontium (88Sr) and zinc (66Zn) in a knee cartilage section from a patient diagnosed with osteoarthritis. (Source: University of Technology Sydney)

Figure 5 illustrates the concept of ablation of the sample together with a film containing an internal standard. Quantitative data is produced by comparing the ratio of the trace elements in the tissue sample to that of the internal standard with the ratio obtained from spin coated slides with a known amount of trace element. This approach generates calibration curves that compensate for the differences in instrumental drift and the efficiency of transfer of the ablated material to the ICP-MS.

Trace elements play a key role in a wide range of biological processes. A full understanding of those processes requires knowledge of the genomics and proteomics of the organism, as well as the distribution and concentration of trace elements.

LA-ICP-MS may be utilized for the in situ analysis of trace metals in biological tissue. Using Elemental Bio-Imaging, isotope-specific maps of the spatial distribution of trace elements, particularly metals within thin tissue sections can be constructed. These images may be employed to probe the mechanism of many diseases in which metals are suspected to be involved such as Parkinson's disease and Alzheimer's disease. **PA**

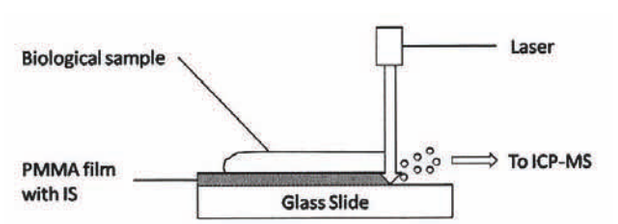


Figure 5: Internal standard scheme for elemental bio-imaging. (Source: University of Technology Sydney)

In collaboration with Agilent Technologies, the University of Technology Sydney (UTS) has established the Elemental Bio-imaging facility, a research effort utilizing laser ablation-ICP-MS (LA-ICP-MS) to study trace metals and other elements in tissue, and their effects on health.

UTS is providing the facility and scientific staff to perform the research to develop this application of ICPMS, and Agilent is providing the instrumentation, as well as funding for project work and postgraduate student support.

Enquiry code: 096E01

Outsourcing in China and India: A Comparison

Contract Research Organizations (CROs) in China and India offer a low cost alternative for pharmaceutical companies that are looking to outsource R&D activities.

Jim J Zhang,
president and MD,
JZMed;
Jiawen Shen,
University of Science and Technology Beijing

The global pharmaceutical industry is facing a number of challenges. Companies today need to pursue more efficient, cost-effective and productive ways to conduct their operations, whether in R&D or manufacturing. The key to a quick turnaround is to have drugs discovered quicker, developed faster, manufactured cheaper and marketed more widely.

Outsourcing is one method that helps drug companies by providing them with the desired efficiency, flexibility and agility. Among the emerging countries, China and India have risen rapidly in the global pharmaceutical outsourcing arena, as both countries possess the unique combination of low cost and quality service. The current global financial crisis has also enhanced the importance of these two countries to many drug companies around the world that are seeking cost reductions.

China and India each possess their own unique features and characteristics, not only in the pharma-related industries but also in almost every aspect of the social structure. To many companies that are interested in conducting outsourcing or looking to invest in either of these countries, it is a challenge to decide on the one that best fits the company's investment goals.

Among the emerging countries, China and India have risen rapidly in the global pharmaceutical outsourcing arena, as both countries possess the unique combination of low cost and quality service.
(Source: China Pharmaceutical Group)

Compare and Contrast

An in-depth study was conducted for the comparison of pharma outsourcing service industries between China and India. This article summarizes the results in a number of areas. It reveals the similarities and differences between these two countries, their advantages and disadvantages in pharma outsourcing, and their strengths and weaknesses in service capabilities.

The investigation of the pharma outsourcing industries in both countries was conducted on the top 50 outsourcing service providers in each country. Detailed comparisons were made between these selected companies in more than ten different areas:

- Advantages and disadvantages of each country in pharma outsourcing;
- Strength and weakness of each country in traditional pharma industry;
- Strength and weakness of each country in biopharmaceutical industry;

Drug Development

- Each country's R&D capabilities in innovative medicines;
- Development history and pattern of pharma outsourcing industry in each country;
- Current market sizes and their shares in the global pharma outsourcing industry;
- Overall service capabilities of each country;
- Service features of each technical sector in each country;
- Cost structures;
- Global presence

China and India are similar in many aspects. Both are located in Asia and are among the most populated countries in the world. Both are still developing countries with low wages for most workers in many industries. The countries offer significant cost-reductions for drug R&D and manufacturing as compared with countries in the west. Both countries now have an acceptable Intellectual Property (IP) protection environment, which is the direct result of the government efforts in both countries.

However, there are also significant differences between these two countries pertaining to pharmaceutical industry.

Largely due to the difference in each country's history in general, the standard of English in Indian companies is better than that of their Chinese counterparts. The formers' business operation style and philosophy are closer to those of western countries.

Indian companies also tend to be more familiar with western regulations than Chinese companies. They also tend to have more extensive global operations. China however, is better equipped in terms of industry infrastructure. The Chinese pharmaceutical market is also much bigger than India's.

China's total pharmaceutical market was valued at about US$68 billion in 2008. It was composed of three parts: western-style medicines that are chemically synthesized small molecule drugs; biologics drugs; and Traditional Chinese Medicine (TCM). In comparison, India's pharmaceutical market was worth about US$14 billion. China's biotechnology industry is more advanced and its education standard in biology is of a higher level.

China's total pharmaceutical market was valued at about US$68 billion in 2008

Strengths and Weaknesses

In pharma outsourcing industry, the combined service scope in each country spans the entire value chain of drug R&D and manufacturing. However, neither country's CROs/CMOs are able to provide fully integrated services at present. There are also differences between the service sectors of these two countries.

In target identification and validation as well as their related areas such as genomics and proteomics research, Chinese companies possess stronger service capabilities than Indian companies. Among the top 50 players in each country, twenty Chinese companies offer good quality services in these areas; whereas only thirteen Indian companies possess similar capabilities.

In drug discovery which primarily includes medicinal chemistry research and heavily involves the generation of IPs, Chinese and Indian companies possess similar skills in rational drug design and optimization, and offer similar services and quality.

For preclinical research, Chinese CROs (Contract Research Organizations) provide better services than Indian CROs. There are 21 Chinese CROs that offer a variety of services in this area. Nine of them also have capabilities in in vivo efficacy testing for non-human primates. Although India has eighteen CROs, none of them offer the service of efficacy testing in non-human primates.

In clinical research, the situation is just the opposite. There are 20 Indian CROs that are qualified to enter the list, compared to only 12 Chinese companies. Moreover, four Indian CROs offer central lab services; whereas none of Chinese-run CROs currently possess the same service capabilities.

In major Chinese pharma companies, a large portion of their on-going internal R&D efforts are focused on the development of generic drugs that are targeted at the domestic market.
(Source: China Pharmaceutical Group)

In process R&D and contract manufacturing, both countries possess similar capabilities. However, Indian companies have better skills and capabilities in formulation and the manufacturing of small molecule drugs.

Chinese companies are more capable than Indian companies in the large scale manufacture of macro compounds such as vaccines, antibodies, recombinant proteins, small interfering Ribonucleic Acid (siRNAs), etc. There are 15 Chinese companies that possess such capabilities; whereas only six Indian companies offer similar services.

Traditional Pharma Companies Involved in Outsourcing Service

In the traditional pharma sector (generic drug manufacturing), there are more major Indian pharma companies that are involved in outsourcing service than Chinese companies. While there are 28 major Indian pharma companies that are qualified to be in the top 50 list, only 14 major Chinese pharma companies made it into the list. Many Indian pharma companies are actively seeking outsourcing opportunities in overseas markets, whereas their Chinese counterparts are more passive. In terms of global presence, 13 Chinese companies have products marketed in overseas markets compared to 30 Indian companies. Moreover, most Indian companies market their products in the well-regulated western markets and a higher proportion of their products are made up of dosage form medicines. In comparison, almost all Chinese pharma companies market their products mainly in less regulated markets, with the majority of these products being Active Pharmaceutical Ingredients (APIs).

Biotech Companies in Outsourcing

Among the top 50 Chinese companies, eight of them are biotech companies, compared to six Indian companies. China has advantages over India in biotechnology in areas such as molecular biology, gene therapy and genomics and proteomics research. Chinese biotech companies have successfully developed a variety of innovative biologics medicines. An example is the world's first cancer gene therapy drug, Gencidine, a recombinant human Ad/p53 injection.

The Chinese government has identified biotech as one of the high-priority industries in the country for future development. In its 12th Five-Year Development Plan, the Chinese government has outlined a series of detailed blueprints to guide its future development including the promise of greater investment.

The biotech industry in India is still in an early development stage. However, the government also supports and promotes the development of this industry. For example, the Indian government plans to launch twenty biotech parks by 2010. At present, India has four biotech parks, mostly concentrated in Hyderabad and Gujarat. The country's central bank has also reduced its loan interest rates to allow small biotech firms to have better access to funds.

Drug Development

Among the top fifty players in each country, the number of Chinese and Indian companies that possess internal R&D programs are the same (twenty in each country). However, their research focuses and capabilities are different.

The R&D programs in many Indian companies focus on small molecule drugs. Generally, starting with well-validated therapeutic targets, their primary strategies are to conduct structural modifications on those known or approved drug molecules, hoping to improve the latter's activity profiles. At present, eight Indian companies in the list have drug candidates in late development stages.

Several major western pharma and biotech companies have in-licensed promising drug candidates from Indian companies. A couple of years ago for example, Novartis licensed an anti-diabetic drug (DRF 4158) from Dr Reddy's Lab.

A number of Indian companies including Dr Reddy's, Ranbaxy and Nicholas Piramal, have converted their R&D-divisions into independent, R&D-oriented biotech companies.

Domestic Marketing

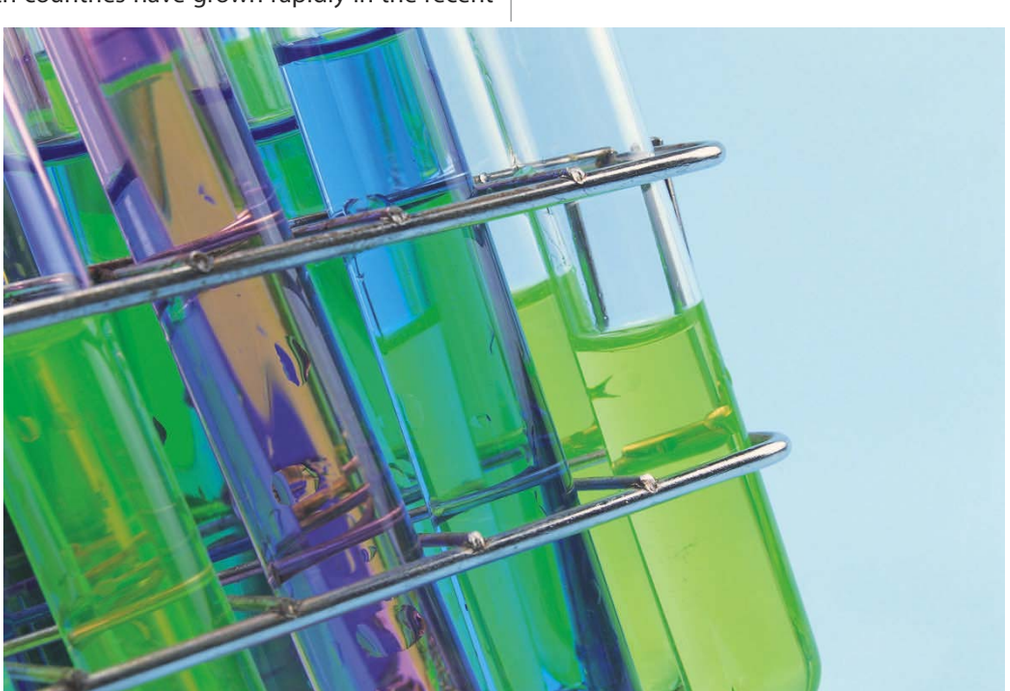
The R&D activities in Chinese companies are more diversified. In major Chinese pharma companies, a large portion of their on-going internal R&D efforts are focused on the development of generic drugs that are targeted at the domestic market. Only a handful of Chinese companies are conducting R&D programs that are similar to those of Indian companies. Examples include Jiangsu Hengrui Medicines and Hutchison MediPharma. At present, full-scale R&D programs of small molecule medicines in most Chinese companies are still in the early stages. So far no drug candidates discovered and developed by the companies have been out-licensed to western pharma companies (although this is expected to happen in the near future).

The unique R&D capabilities of Chinese companies are in the research, discovery and development of macro compound-based medicines such as recombinant proteins and siRNAs. Examples include Shenyang Sunshine Pharma and Shanghai Sunway Biotech, both focusing on the R&D of proteins such as therapeutic tools.

The pharma outsourcing industries in both countries have grown rapidly in the recent few years. They are currently valued at about US$1.42 billion for China and US$1.77 billion in India, with both occupying only about a two percent share in the global outsourcing market – although both markets are poised for rapid growth in the future. However, China appears to have a higher future growth potential compared to India as it has fewer growth resistors. The former's outsourcing market is likely to catch up with and surpass India's after 2010.

Investment Strategies

Major western pharma and biotech companies adopt different strategies in these two countries. In India, they tend to form close collaborations such as risk-sharing outsourcing with an Indian company to co-develop drug candidates – but few of them are willing to permanently set up larger R&D centers or manufacturing facilities in the country.



The unique R&D capabilities of Chinese companies are in the research, discovery and development of macro compound-based medicines such as recombinant proteins and siRNAs.

In contrast, a number of these major companies have invested several hundred million dollars in China to establish their wholly-owned R&D centers, large scale manufacturing and even marketing facilities. Many of these centers are now ready to conduct full-scale research independently.

At present the R&D centers belonging to major pharmaceutical companies are typically staffed by 300-500 researchers. For example, the Shanghai R&D centers of both GSK and Novartis have about 500 scientists. Pfizer's Shanghai center has about 350 scientists. Roche's R&D center in the same city has just over 200 employees.

The outsourcing models between western companies and Asian companies are also not limited to just R&D. They have also been extended to include various types of activities such as product marketing and drug candidate licensing.

Ortho-McNeil Jassen Pharmaceuticals (OMJPI), a subsidiary of Johnson & Johnson has (almost) simultaneously signed separate outsourcing deals with a Chinese company and an Indian company (Table 1).

Items compared	Chinese company: Hutchison MediPharma	Indian company: Advinus Therapeutics
Date	December 2008	November 2008
Contract value	No details were disclosed but Hutchison will receive an upfront payment. It will also have milestone payments, royalties and rights to market drugs developed in China, to countries including Hong Kong and Taiwan.	A total of US$247 million including milestone and royalty payments.
Therapeutic targets	Immunology, inflammation.	Metabolic diseases, inflammation.
Collaboration details	Hutchison is responsible for discovery and development up till early stage clinical trial (Proof-Of-Concept). OMJPI will take over the drug candidates and further develop them until commercialization.	Advinus is responsible for discovery and development until phase IIa (Proof-Of-Concept). OMJPI will then take over and further develop them until commercialization.

Table 1: Head-to-head comparison of outsourcing models of Ortho-McNeil Jassen Pharmaceuticals with a Chinese company and an Indian company

These two outsourcing collaborations indicate that western companies are increasingly utilizing CROs in emerging countries particularly in China and India as the extensions of the former's R&D divisions. This demonstrates the growing level of trust in such companies for drug R&D.

China and India have become the two most popular countries for outsourcing. However, each country possesses its own characteristics and offers unique services. It is important for outsourcing companies to understand these differences.

At present, India is more advanced in small molecule drug R&D and manufacturing. China has achieved stronger competencies in biotechnology including the R&D and in the manufacturing of macro compounds. India offers better product quality while China is able to provide a higher cost reduction. **PA**

Enquiry code: 09602

Drug Development

Pharmaceuticals R&D in Asia: On the Move (Part One)

Western pharmaceuticals companies are increasingly looking eastward to relocate their R&D activities.

Frank Floether,
VP business development
Asia Pacific (2004 – 2008),
Johnson & Johnson

The focus of the global pharmaceutical industry is shifting, with Asia set to be the largest pharmaceutical market in the world. With the expansion of low cost manufacturing in the region, companies are seeking to site research, development, analytical services and clinical trial activities in Asian territories.

This reflects both increased capabilities in the region and a changing business model for pharmaceutical Multinational Companies (MNCs). The view that the center of the industry is moving away from North America and Europe and towards Asia is shared by MNCs and Asia-based companies alike. About 50 percent of MNCs agreed with that statement and less than a quarter voiced any disagreement with the prospect of such a shift, according to Price WaterhouseCoopers.

With the expansion of low cost manufacturing in the region, companies are seeking to site research, development, analytical services and clinical trial activities in Asian territories.

Relocation

Historically, the pharmaceutical industry has been slower to embrace offshoring. However, this trend has started to change with significant movement towards global sourcing over the last few years. Unlike many other industries, the pharmaceuticals sector is uniquely positioned to remotely execute one of its core competencies, ie, R&D, which represents 74 percent of offshore employment.

Part of that change is the recognition that one of the key challenges of the biopharmaceutical industry is to improve R&D productivity. Organizations are targeting the drivers of cost and value, aiming to increase R&D productivity through a series of lines of attack – offshoring is one such approach.

For reasons such as strategic importance and market size, the Asian countries of choice are particularly China and India.

India, China and Singapore are poised to become leading countries in the Asia pharmaceutical space – other territories, notably South Korea, Malaysia and Thailand are also building domestic pharmaceutical bases although the MNCs currently dominate these markets at this stage.

The Boston Consulting Group stated in 2005, that for the top ten MNCs, total sales in China during 1999-2004 registered a compound annual growth rate of 15 percent. By the year 2010, China will probably have leapfrogged major European markets to become the world's fifth-largest national market for pharmaceuticals, with sales likely to reach US$25 billion – almost double the current total.

Many MNCs are intensifying their market efforts by investing in commercial operations. A main reason for investing in R&D activities in China and India is the cost factor. These companies face increasing developmental costs (more than US$1.0 billion) while being pressurized from health authorities to decrease prices. This has given rise to a cost-driven shift towards outsourcing to low-cost countries, in particular to Asia.

Pharmaceutical MNCs from a variety of industries expect that just relocating lab work and even more clinical trials from the West will reduce bills, rentals and overhead by half.

Trade-Off

There are however, other factors to consider. Offsetting costs arise from relocating the necessary existing staff, importing equipment and supplies, and maintaining equipment. This is in addition to the impact of possibly lower productivity and security, differences in technical practices, regulatory and legal requirements, culture and language.

However, cost savings alone are not the primary consideration for the pharmaceutical industry. Because of the expected rise in wages of highly-skilled employees, the increasing costs of support functions and compliance in Asia, focusing on cost advantage is a short-sighted view.

The true value of conducting R&D in India and China lies elsewhere – as a strategic lever for helping companies to achieve their Asian ambitions. When MNCs conduct such activities in India and China, they have the opportunity to increase their own visibility and reputations. This will help them to shape these domestic health-care markets and to consolidate their own market share.

Another aspect is the huge and expandable talent pool. In addition to having a huge output of high-quality locally trained scientists, India and China have an impressive and steadily increasing number of scientists. These skilled labor have returned in recent years with master and doctorate degrees that were earned overseas.

The fact that the Intellectual Property Rights (IPR) situation was adapted to international standards (India recognizing full product patents on pharmaceuticals in 2005; China's entry into the World Trade Organization, WTO, in 2001) has further enhanced the dynamics in setting up a strategic R&D presence of pharmaceutical MNCs.

In summary, most of the pharmaceutical MNCs move East for the following reasons: strategic presence facilitating growth in emerging huge markets; cost savings; capacity constraints in the West; and developing products in close proximity to local markets.

About 80 percent of the Active Pharmaceutical Ingredients (APIs) for drugs that are made in Europe, are manufactured in India and China. In addition, 30 percent of bulk drug manufacturing – worth around US$31 billion, and US$25 – US$30 billion for pharma R&D are outsourced by major global players, according to the Economic Times, India in 2008.

Offsetting costs arise from relocating the necessary existing staff, importing equipment and supplies, and maintaining equipment.

"Big Pharma" Challenges – Reasons for Heading East

The challenges that are faced by current Big Pharma companies can be summarized as:

• Increasing cost of drug discovery & development due to:

- Tougher regulatory demands.
- Competition for patients.
- Larger clinical studies.
- High rate of failures.
- New technologies not yet paying out (eg: genomics).
- Longer development timelines.

• Increasing time-to-market. For instance, a delay in the launch of a drug can cost a company up to US$23 million per day in terms of lost sales in the US alone, and almost US$37,000 per day in terms of additional development costs, according to Datamonitor, 2008.

• Impending patent expirations of blockbuster molecules. For example, a large percentage of Big Pharma revenues are at risk as drugs that worth US$47 billion are expected to go off–patent in the US alone over the next 3 years.

• Pricing pressure in the US and Europe (by the government to reduce health care costs).

• Increased penetration of generics.
• Considerable reduction in the numbers of new product approvals. In 2007, the US Food and Drug Administration (FDA) approved just 19 new drugs, the lowest in 24 years.
• Low public opinion.
• Increasingly aggressive generics companies.
• Re-importation pressures.

In consideration of these issues, MNCs need to radically rethink their strategic options and business model, ie, ways to maintain revenue, increase productivity, and lower unit costs.

Offshoring R&D has already proven beneficial and even essential in comparable high-skill industries such as the software industry. Global resourcing of R&D can help pharma companies to unlock productivity gains.

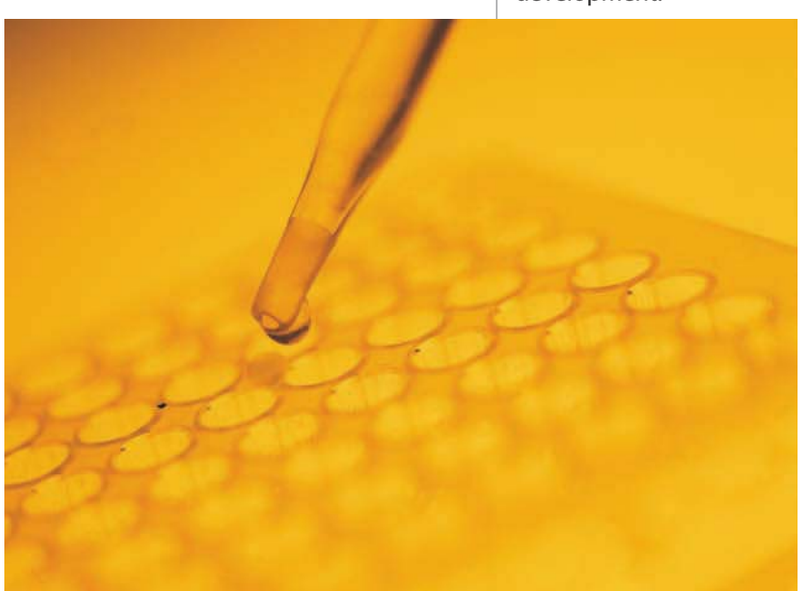
R&D offshoring can serve a number of purposes. It can help to improve global cost structures and counterbalance reduced growth rates in the West via:

• Early access to emerging markets
• Supporting MNCs' sustainable growth in big Asian economies
• Accelerating launches, eg, by tapping into large and naive patient populations
• Faster enrolment into clinical studies
• Building new growth platforms
• Capitalizing on Asian talent pools and innovation potential
• Utilizing "reverse brain drain" by hiring returnees in their respective Asian countries
• leveraging on highly developed IT and bioinformatics (India)

India as an Offshoring Destination

There are three area's of concentration of Pharma R&D (service) activities in India: Mumbai, Hyderabad and Bangalore.

India has a highly developed and relatively mature domestic pharmaceutical industry, which is still mainly geared towards generics. Although most advanced Indian companies continue to strengthen their generics franchises and are on their way to become global players, they have set off to change business models and strategies towards New Molecular Entity (NME) development.



Because of the expected rise in wages of highly-skilled employees, the increasing costs of support functions and compliance in Asia, focusing on cost advantage is a short-sighted view.

The strong interest of Indian pharmaceutical companies in collaborations and alliances with Western MNCs offers opportunities to create "win–win" situations for both parties. Substantial cost advantages for Western pharmaceutical companies by doing business in India are only one benefit for MNCs.

Indian companies are not just offering world-class manufacturing services, both in finished products and in particular in API sector, but also in R&D.

For medicinal chemistry work within the R&D sector, chemistry process research and clinical testing have been the strongest areas. However, chemical and pharmaceutical development including comprehensive analytical services is also emerging.

Up till now, Indian companies have focused on developing drugs "faster and cheaper" and on deploying their capabilities in chemistry research, clinical trials and manufacturing oral solids. The second phase, expected over the next five years will extend capabilities to include the complex manufacturing of injectables, clinical trials (including proof of concept trials), and more sophisticated biology-based research platforms.

The third lap will likely occur between 2013-2015, when Indian companies are expected to start manufacturing biologics and offer cutting-edge R&D platforms such as cheminformatics.

These activities (including achieving the respective cost advantages) can be accomplished by various operating models: Collaboration with Contract Research Organizations (CROs) / Contract Manufacturing Organizations (CMOs), joint ventures between Indian pharma companies and Western MNCs and MNCs that are setting up their own facilities.

Better Intellectual Property Rights (IPR) protection, an English speaking workforce, a relatively small time difference with Europe and political stability are additional supportive factors for MNCs to set up their own offshoring R&D capabilities in India, or to collaborate with Indian companies.

For chemical and pharmaceutical development activities in full Good Manufacturing Practice (GMP) up to pilot scale, India is by far the preferred Asian destination.

There are however certain disadvantages in investing in India:

o Lack of attractiveness for expatriates.

o Less developed infrastructure.

o Generics mindset.

o A lack of certain skill sets (quality assurance, maintenance). **PA**

Part two of this series will be featured in the October issue of PharmaAsia and will focus on the Chinese market.

Enquiry code: 096E03

Drug Delivery

Personalized Medicine for Cancer Treatment

Pharmacogenetics aids in the selection of the right therapy…for the right patient.

Ahmad R Utomo,
PhD, Manager,
Stem Cell and Cancer Institute and
Kalbe Genomics Laboratory

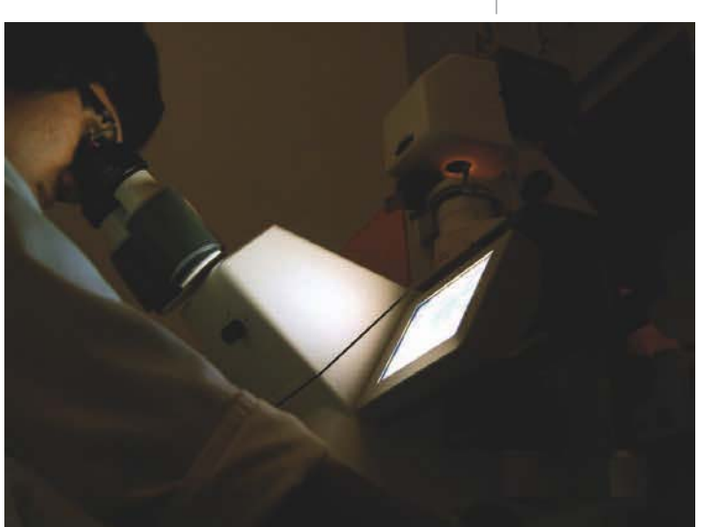
Pharmacogenetics is generally regarded as the study or clinical testing of genetic variations that contribute to differing responses to drugs. Emerging evidence also show the presence of inter-ethnic variations in terms of the specific identity and/or the prevalence of pharmacogenetic markers that are found in populations living in different geographic areas. In cancer treatment, the application of pharmacogenetics can be applied in three areas: avoidance of Adverse Drug Reactions (ADRs), selection of treatment options, and prediction of recurrence probability.

Genetic Variation

Recent advances in medical genetics may add a precise healing touch where doctors pay careful attention to the unique genetic makeup of each of their patients. Although this genetic variation among patients is well-known, the relevance of this information in cancer treatment is only just being appreciated. It is known that genetic variation is an important cause of varying responses and outcomes in cancer treatment.

Furthermore, not all cancers are the same, since malignant tumors with identical tissue of origin can have a heterogeneous genetic portrait. Therefore, pharmacogenetics is a study that seeks to understand genetic contribution, which stimulate varying responses to a certain drug.

The immediate aim and application of the pharmacogenetic approach of cancer treatment is in matching the right patients with the right drugs. This is to avoid adverse drug reactions while selecting the best treatment strategy, while improving the predictive ability to foresee cancer recurrence in a given genetic profile.



The application of pharmacogenetics in cancer treatment is a promising approach that has altered certain practices especially in the management of colorectal, lung, brain, and breast cancer. (Source: Kalbe Farma Tbk)

Furthermore, one must also bear in mind the presence of genetic variations across different ethnic populations. Many pharmacogenetic research studies have been performed on Caucasian or white-European populations and have yielded a number of genetic biomarkers with assigned functions and consequences.

While cancer is the unifying nemesis of all ethnic groups, the underlying ethnic-dependent genetic variation may also result in different cancer phenotypes and behaviors. For instance, genetic studies of hereditary breast cancer show that the mutation of Breast Cancer Susceptibility Gene-2 (BRCA2) is more prevalent in Asian patients compared to European patients. BRCA1 mutation is more common in the latter.

With increasing incidences of cancer in the Asia Pacific Rim which is projected to see 8.1 million new cancer cases in 2020 compared to 3.5 million in 2002, there is a need for more effective cancer management. Pharmacogenetics may contribute to improved effective cancer management, but its application must also address the specific identity of and the prevalence in relevant genetic biomarkers. This is in addition to other socioeconomic factors such as diagnostic costs, liability issues, insurance reimbursement and the involvement of regulatory agencies.

Avoiding ADR

Colorectal cancer ranked fourth in Asia and its growth is alarming. Up to 15 percent of colorectal cancer patients are treated with a combined chemotherapy of Irinotecan, Leucovorin, and 5-Fluorouracil (5-FU). Patients who receive chemotherapy have to experience Adverse Drug Reactions (ADRs), which ranks number four as the cause of death in the US.

Irinotecan is given as a prodrug that is converted into an active metabolite SN-38 by an enzyme carboxylesterase. SN-38 cytotoxicity is 1000 times more potent than the prodrug. In the body, the metabolite is rendered inactive by a process called glucuronidation, which is an important detoxification process. The glucuronide derivative of SN-38 is SN-38G, which is produced by several hepatic and extrahepatic Uridine diphosphate Glucuronosyltransferase (UGT) enzymes, whose major isozyme is UGT1A1.

Individuals who inherit the polymorphic forms of UGT1A1*28 alleles suffer from Gilbert's syndrome. They are particularly susceptible to adverse reactions of irinotecan (such as neutropenia and diarrhea) due to the relatively high level of and/or prolonged exposure to the highly cytotoxic active form of the drug. The principal cause is a reduction in hepatic bilirubin glucuronidating activity to about 30 percent of normal levels.

Interestingly, the associated Irinotecan ADR in Asian subjects is linked to UGT1A1*6 and rarely to UGT1A1*28. Therefore, testing for the UGT1A1*28 allele for the purpose of Irinotecan dosing may be appropriate for only a certain population.

The pharmacogenetic approach may also be applied in predicting five-fluorouracil (5-FU) toxicity, a common and important chemotherapeutic agent against colorectal cancer. It acts principally by inhibiting thymidylate synthase, a rate-limiting enzyme in pyrimidine nucleotide synthesis.

Five-fluorouracil (5FU) is primarily degraded by Dihydropyrimidine Dehydrogenase (DPYD). Partial loss of the enzyme due to specific alelles (IVS14+1 G > A, DPYD*2A) may be partly responsible for 5-FU induced toxicity. Caucasians have such a mutation with a frequency of 1-2 percent in the general population. However, studies in Asian patients have not yielded the same allele of DPYD as found in the Caucasian population.

Treatment Selection

The majority of human epithelial cancers are marked by the functional activation of growth factors and the EGFR (Epidermal Growth Factor Receptor) family. Four EGFR antagonists, ie, Cetuximab, Panitumumab, Erlotinib and Geftinib are currently available for the treatment of four metastatic epithelial cancers, ie, non-small cell lung cancer, squamous-cell carcinoma of the head and neck, colorectal cancer, and pancreatic cancer.

A number of retrospective studies have revealed that the response rate of anti-EGFR agents given as monotherapy in unselected patients is generally around 10 percent. Interestingly, molecular studies focusing on the downstream signaling of the EGFR pathway revealed that mutation in the V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (K-RAS) and EGFR cytoplasmic domain can affect therapeutic outcomes in colorectal and lung cancers. Colorectal cancer and lung cancer patients whose tumors bear the K-RAS gene mutation do not benefit from Cetuximab or Erlotinib based therapies.

On the other hand, up to 40 percent of patients whose tumors have the normal K-RAS gene have responded to this anti-EGFR treatment. In Asia, several studies have shown that the prevalence of KRAS mutation in colorectal cancer is around 30 percent, which is 10 percent lower than European or North American patients. A similar trend is also found in lung cancer, where the prevalence of K-RAS mutation is around 10 percent in Asian patients, compared to 30 percent in Caucasian patients.

In addition to genetic biomarkers (such as polymorphisms and mutations), there is also an epigenetic biomarker that has been linked to a therapeutic outcome of alkylating agents as in the case of Glioblastoma. Deoxyribonucleic Acid (DNA) methylation is an example of epigenetic

A number of retrospective studies have revealed that the response rate of anti-EGFR agents given as monotherapy in unselected patients is generally around 10 percent.

processes where aberrant insertions of a methyl group at the fifth carbon of cytosines within the dinucleotide CpG islands located at the promoter region of specific genes, cause the suppression of gene expression.

The most extensive evidence that DNA methylation markers can predict chemotherapy responses is provided by the O6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation in glioblastoma. MGMT plays a crucial role in defense against alkylating agents and is thought to be the resistance factors in Glioblastoma.

A study reported in 2005 showed that temozolomide's efficacy is associated with the MGMT promoter methylation status of glioblastoma patients. The difference between the overall survival of the non-methylated MGMT promoter group receiving temozolomide plus radiotherapy and those receiving radiotherapy alone was statistically not significant.

On the other hand, the overall survival of the methylated MGMT promoter group receiving temozolomide plus radiotherapy, was significantly better than those who received radiotherapy alone. In other words, for patients with the methylated MGMT gene, the median survival was 21.7 months when treated with temozolomide and radiotherapy as compared with 15.5 months among those who were treated with only radiotherapy.

Therefore temozolomide, which is given after radiotherapy, may be beneficial to glioma patients with the methylated MGMT promoter, but not to those with the unmathylated promoter. The prevalence of the MGMT promoter methylation has been documented for 30-40 percent of glioblastoma patients. Limited reports from Japanese and Korean groups have also indicated similar prevalence in their patients.

Improvement of Prognostic Ability to Predict Recurrence

Besides the predictive genetic and epigenetic biomarkers (K-Ras mutation and MGMT methylation) that have been explained previously, prognostic biomarkers are also crucial in determining the patients who need chemotherapy. Such biomarkers predict the clinical outcome for a patient if no anticancer drugs are administered. Anticancer drugs such as adjuvant therapy, are often given to patients after they undergo tumor resection. Unfortunately, it is not always clear as to who actually, among these patients, needs adjuvant therapy.

The introduction of DNA-microarray technology has made it possible to assess the expression of multiple genes in a single experiment. Patterns of gene expression that are associated with a specific clinical outcome called Signature, can be identified systematically.

The 70-gene signature microarray has been developed for predicting breast cancer prognosis. The 70-gene expression profile discriminates between a good and a poor outcome in patients with early-stage breast cancer, irrespective of their hormone status of estrogen and progesterone receptors. This 70-gene expression profiling, also known as 'Mammaprint,' is one of the most well-validated prognostic tools. It has been commercialized by Agendia and has been approved by the US Food and Drug Administration (FDA). It showed 77 to 81 percent agreement in outcome classification.

Therefore, patients with good prognosis are saved from having to undergo chemotherapy and are able to avoid unnecessary side effects. The effectiveness of this 70-gene profile as a prognostic tool has been currently undergoing a clinical trial in Japan since early 2009. The anticipated result may shed light on whether it is an effective tool to predict recurrence in Asian breast cancer patients. Moreover, a significant portion of Asian breast cancer patients who are largely Estrogen-Receptor (ER) negative may benefit from this microarray based diagnostic test.

The application of pharmacogenetics in cancer treatment is a promising approach that has altered certain practices especially in the management of colorectal, lung, brain, and breast cancer. Nevertheless, the awareness of the different identities and the prevalence of relevant genetic and/or epigenetic biomarkers in different ethnic groups is important in making pharmacogenetics an effective approach. **PA**

Enquiry code: 096E04

The immediate aim and application of the pharmacogenetic approach of cancer treatment is in matching the right patients with the right drugs. (Source: Kalbe Farma Tbk)

PCR Technology for Flu Surveillance

Rapid, sensitive and accurate testing is needed to combat and contain the influenza H1N1 virus.

Finn Zedler,
Director of Molecular Diagnostics, Asia,
Qiagen

When the Influenza A / H1N1 virus (commonly referred to as the Swine or Mexican Flu) scare hit its peak at the end of April 2009 through the beginning of May, researchers and lab workers were under increasing pressure to step-up and improve surveillance and testing methods.

The fast and reliable detection of potential infections is imperative to contain the dissemination of epidemics – be it Swine Flu, Avian Flu or Severe Acute Respiratory Syndrome (SARS). However, the two currently most widespread technologies for the detection of viral infections do not appear to be fully meeting the requirements of modern diagnostics – where global travel is commonplace and the outbreak of the next pandemic threat is only a matter of time.

The aforementioned screening methods for influenza are viral cultures and are called rapid diagnostic tests. As with many other viruses, a viral culture, or growth assay, is considered the "gold standard" of influenza testing. Using this technique, a live culture of a susceptible cell line is inoculated with the virus (or the unknown specimen for diagnostic purposes).

Under defined and controlled laboratory conditions, the virus replicates in the cells. Amplified amounts of the virus can then be isolated after a few days of growth for further analysis. While a viral culture is definitive, it is also time intensive, with results taking up to 10 days to generate.

This may be a significant limitation especially regarding fast-response strategies to pandemic threats. In addition, viral culture is expensive and requires a high level of expertise as well as special biosafety facilities. Hence, the viral culture may not be the method of choice for clinical diagnostics in routine diagnostic labs. Rather, it is predominantly performed in reference labs and virology centers as a confirmatory or reference method, or for retrospective assessment and epidemiological studies and research.

The fast and reliable detection of potential infections is imperative to contain the dissemination of epidemics

The second method includes the use of Enzyme Immunoassays (EIA) and Direct Immunofluorescence Assays (DFA). These serologic tests take advantage of the specific binding of an antibody to its antigen, and in the case of the Swine Flu, the detection of specific antibodies against influenza in the serum of the patient.

In principle, the assays contain some kind of viral antigen; either complete virus particles which are commonly used in DFA, or viral proteins used in EIA. Such antigens specifically capture influenza-antibodies from a seroconverted, or influenza positive patient. In a second step, these Influenza-antibodies are detected by an enzymatic reaction after a second antibody, specific for the influenza-antibody from the patient sample, has been added to the reaction.

These tests are widely used in clinicians' offices due to the former's relatively low costs, fast time-to-results and easy handling. However, there is also a reason for caution. Generally, the better assays of this group have a reasonably good specificity – the proportion of correctly identified negatives is above 90 percent versus viral culture. This means that a high percentage of negative results with the rapid test are also negative by viral culture.

In contrast, sensitivity – the proportion of correctly identified positives of rapid tests is only about 70 percent compared to viral culture. For example, three out of 10 patients may get a

Drug Delivery

negative result with a rapid test (but would have tested positive in viral culture), and hence be incorrectly reported as negative.

This lack of sensitivity or high percentage of false negative results makes it difficult to effectively contain possible viral outbreaks, as a significant number of infected patients cannot be identified, separated and treated appropriately.

Molecular diagnostics technologies which screen for the presence of genetic material from defined pathogens, provide a hope for the effective containment of current and future viral outbreaks. The technology that serves as the base for these tests is the Polymerase Chain Reaction (PCR).

Unlike serologic rapid tests, molecular assays detect the antigen, in this case, the influenza virus itself, rather than the humoral response of the patient's immune system – the anti-Influenza antibody. Every species on the planet has a unique and specific genetic code. By targeting these genetic codes, or rather their molecular components Deoxyribonucleic Acid (DNA) or Ribonucleic Acid (RNA), molecular tests overcome some of the limitations of the earlier-mentioned technologies.

The advantage of PCR and its variant Reverse Transcription-PCR (RT-PCR) tests, is that they are rapid, sensitive and highly specific. PCR is an enzymatic reaction that amplifies small copy numbers of specific target DNA sequences to vast numbers of identical copies in generally 35 to 45 repetitive cycles.

RT-PCR uses RNA instead of DNA as a starting material, and in an initial step, converts or reverse transcribes the RNA into DNA. This method is used for the detection of viruses which contain RNA as their genomic material, such as influenza. Both methods are referred to as nucleic acid tests.

Nucleic acid testing provides a tool for the rapid and sensitive detection of various influenza viruses in research applications and routine testing. Beginning with just a small sample of DNA or RNA, the turn-around time for testing is reduced from days and weeks (as required for viral culture) to just hours, while overcoming the low sensitivity of rapid tests. PCR also does not require high-level bio-safety in facilities or extensive skills and expertise.

Nevertheless, PCR results are highly dependent on the purity and quality of the starting materials, for example, the viral nucleic acids in the case of Swine Flu detection. Meaningful results can only be guaranteed if the viral nucleic acids are properly extracted and purified from the patients' samples.

Multiplex assays allow for the simultaneous detection of multiple pathogens from a single sample. Such assays can differentiate between influenza Type A and B and also detect additional respiratory viruses, thereby providing molecular differential diagnoses to lab personnel.

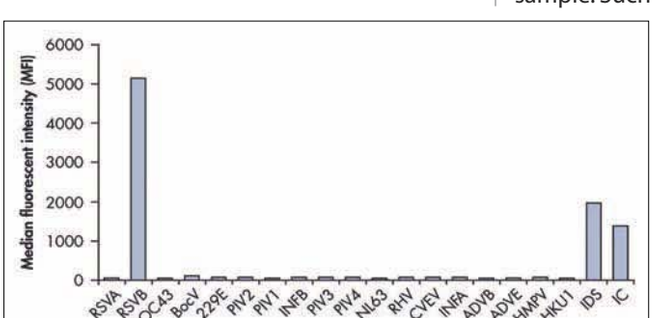


Fig. 1: Multiplex assays allow for the simultaneous detection of multiple pathogens from a single sample. (Source: Qiagen)

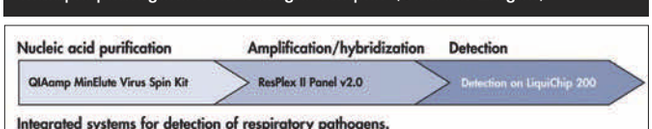


Fig. 2: Integrated systems for the detection of respiratory pathogens. (Source: Qiagen)

Labs no longer need to run a series of subsequent tests to rule out one pathogen after another until a causative agent is established. Information on the presence or absence of 18 different common viral respiratory pathogens can be obtained in a single experiment. (See figures 1 and 2)

The benefits of molecular diagnostic assays have made them a logical choice in disease control and prevention efforts around the world. The successful use of these technologies is particularly evident in Asia as the high population densities pose major challenges to the public health systems in case of a pandemic.

In order to avoid another SARS-like epidemic, China has enacted a strict control and prevention scheme of which RT PCR assays are the backbone. These assays are helping the country to contain the spread of Swine Flu within its borders.

Other countries such as Singapore, have also created strategic stockpiles of assays for pathogens such as Avian Flu. **PA**

Enquiry code: 096E05

Intelligent Sorbents: In-Vitro Diagnostic Applications

Choosing the right sorbent is vital in ensuring the integrity of packaged products.

Adrian Possumato,
global director,
Healthcare Packaging
Multisorb Technologies

Dropping a sorbent into In-Vitro Diagnostic (IVD) product packaging is a method for preventing product damage from moisture, and maintaining shelf life and IVD product accuracy. However, new IVD devices and packaging configurations, coupled with the pressures to speed products to market, often require that sorbents become intelligent.

Rather than simply serving as a moisture absorber, sorbents need to fit the role of environmental managers. This is to provide a specific range or a steady-state level of protection to product packaging that is increasingly taking different and more innovative shapes.

An intelligent sorbent is designed to provide a specific management outcome, which could be controlling the level of moisture, oxygen, and/or hydrocarbons in a product's packaging system. In some cases, it is necessary for the sorbent to carry out multiple protective functions. It might be used to maintain a specific humidity range to ensure a product's stability, or to reduce or eliminate volatilized hydrocarbons.

The IVD landscape has been changing rapidly and packaging solutions are required to become more innovative. In turn, IVD devices in development today are changing the format of the sorbent itself, requiring in some cases that the latter be customized and incorporated into a packaging design much earlier in the process. Manufacturers need to be aware of intelligent sorbent solutions as they struggle to meet the packaging protection needs of IVD technologies in a competitive marketplace.

For products that are subjected to oxidative and moisture-mediated degradation, sorbents can be customized to perform the role of specialty oxygen absorbers. (Source: Multisorb Technology)

Environment Control

For products that are subjected to oxidative and moisture-mediated degradation, sorbents can be customized to perform the role of specialty oxygen absorbers. They can be developed to eliminate oxygen from the packaged environment while managing free moisture and maintaining a specific Equilibrium Relative Humidity (ERH) in the package. This is critical to ensuring the integrity of IVD product compositions that require both oxygen and moisture management.

Another important function of the modern-day sorbent involves hydrocarbon management. Residual solvents from reagents, substrate, and packaging materials can form volatized hydrocarbons that end up in the headspace of a product's package. In addition to potentially destabilizing the IVD product, this can produce a noxious odor that must be removed through the use of activated carbon. In these instances an intelligent sorbent can be tailored to perform the dual function of removing odors while at the same time maintaining moisture control.

It is important to determine the type of hydrocarbon management that is needed for a particular product, as this will

determine an intelligent sorbent's configuration. For example, a sorbent that is made from a specific type of molecular sieve could be configured to function as a hydrocarbon scrubber, which removes volatilized hydrocarbons.

The functionality of the sorbent is dependent on the specific need. In some cases it may be necessary to remove hydrocarbons but to retain water molecules, in which case the sorbent must be constructed so that it does not over-desiccate a product.

It is also the case that requirements may include the management of moisture, oxygen, and hydrocarbons in one solution. In such instances, a specific formulation for moisture regulation is designed to manage to a customized, steady-state equilibrium relative humidity condition. Simultaneously, oxygen is removed from the hermetically-sealed product package and volatilized hydrocarbons are adsorbed.

Finding a Balance

IVD platforms that are coming to the market are often based on fast acting chemistries, each with unique chemical stability challenges. These challenges mean that traditional desiccant products may no longer satisfy the packages' protection needs. With intelligent sorbent technologies, some of these inherently unstable IVD platforms are being stabilized.

The result is increased pressure on analytical chemists and packaging engineers who are charged with keeping IVD products stable. These engineers increasingly need to work with analytical chemists to understand the specifics of the reagents and/or biologically active materials that form the basis of their IVD platform.

Although sorbents are often inserted into the packaging at or near the end of the packaging line, the choice of sorbent strategy cannot be an afterthought. (Source: Multisorb Technology)

In most cases, the goal of a sorbent is to prevent the degradation of chemical reagents and/or biologically active proteins within the product's packaging. An aggressive and active sorbent that dries an environment, works well for some IVD chemistries because it reduces the molecular mobility and inhibits the chemical reactions that can lead to product degradation.

Conversely, over-drying can degrade an IVD product as biologically active proteins can denature if they are over-desiccated. For example, the over-desiccation of certain blood-glucose Over-The-Counter (OTC) test strip platforms can cause physical and aesthetic damage to the substrate, resulting in slower blood sample wicking and related reaction times. In these cases, aggressive moisture management can cause serious problems and skew the result of the blood glucose test.

Early Planning

Given the numerous IVD platforms with different stability challenges that require intelligent sorbents, a one-size-fits-all approach to packaging protection may not be not a viable strategy. A significant number of resources go into packaging, and without careful planning and consideration of all the factors that are required for protecting an IVD product, the result may be a product with compromised stability.

A sorbent packaging strategy must be *intelligent*, and it must be optimized based on the specific application. It must consider the product, its chemistries, instrumentation, and required shelf-life – essentially the entire life cycle of a product from manufacturing to end-use.

A common mistake is to assume that a sorbent's function is simply to absorb or adsorb excess moisture, or that the answer to an unstable chemical compound is to simply insert additional sorbents into a package. Although sorbents are often inserted into the packaging at or near the end of the packaging line, the choice of sorbent strategy cannot be an afterthought. **PA**

Enquiry code: 096E06

Pharmacovigilance in Emerging Markets

National regulators in Asia Pacific are intensifying their efforts to manage the risk of adverse drug reactions.

Dr John McEwen,
Adjunct Associate Professor,
University of Canberra

Pharmacovigilance is subject to a number of developments including electronic reporting, mandatory reporting by companies with registered products (also called Marketing Authorization Holders - MAHs), inspections of pharmacovigilance activities of MAHs, risk management planning, development safety update reports, data-mining and specialized staff training in pharmacovigilance.

As originally set up in many countries, pharmacovigilance depended on the submission of case reports of suspected adverse effects of medicines in individual patients by their doctors, dentists and, generally and more recently, by pharmacists, other health care practitioners and consumers. The reports are sent to national centers, many of which are members of an international collaborative program under the auspices of the World Health Organization (WHO), based at the Uppsala Monitoring Center (UMC), Sweden. This reporting of individual cases remains an essential part of pharmacovigilance today.

Technological Assistance

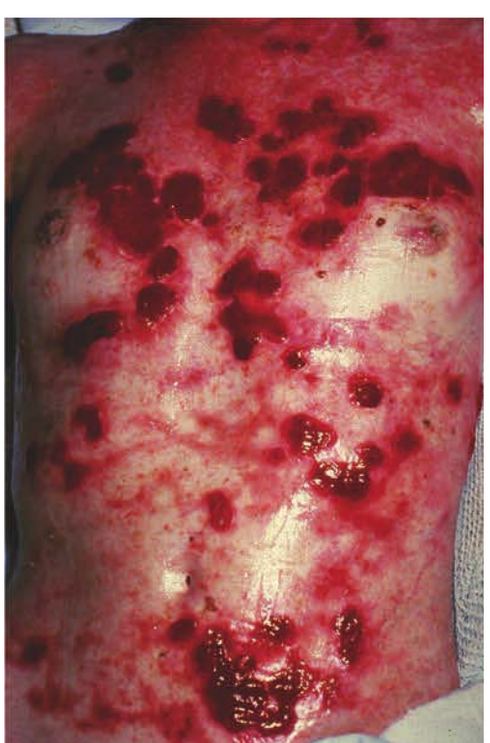
In the more developed countries in the Asia Pacific region (Australia, Korea, New Zealand, Singapore), doctors and pharmacists increasingly utilize computers in their daily work. To capitalize on this, national centers in those countries are introducing electronic methods of reporting, such as web-based report forms and encrypted email reporting.

With the growth of the use of new active substances in the past four decades, many national regulatory authorities have made regulations requiring MAHs to submit reports of individual cases that come to the attention of any of their staff, including those that promote products to doctors. Some regulatory authorities in the Asia Pacific region require reporting by MAHs. Company reports, as a proportion of all reports submitted, vary between Asia Pacific countries, ranging from a few percent to about 85 percent in Japan. It can be expected that as pharmacovigilance assumes greater importance in individual countries in the region, other countries will be likely to mandate the reporting of all, or perhaps only serious cases as they become known to the MAHs.

Concern about compliance of MAHs with reporting requirements has led to the introduction of pharmacovigilance inspections in Europe and the US. In 2007, Australia, New Zealand, Malaysia, Singapore and Thailand did not have a legislated basis for undertaking pharmacovigilance inspections. Australia is in the process of legislating and other regulatory authorities should follow as their laws and resources permit.

The required behavior of companies in pharmacovigilance has been increasingly codified as, for example, in the European Union's "Requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections" (Volume 9A of The Rules Governing Medicinal Products in the European Union).

Two organizations have been involved in the introduction of developments in pharmacovigilance. The Council of International Organizations of Medical Sciences (CIOMS), co-located with WHO in Geneva, has sponsored a series of working parties with broad membership from industry and regulatory authorities to investigate and develop recommendations for innovations in pharmacovigilance.



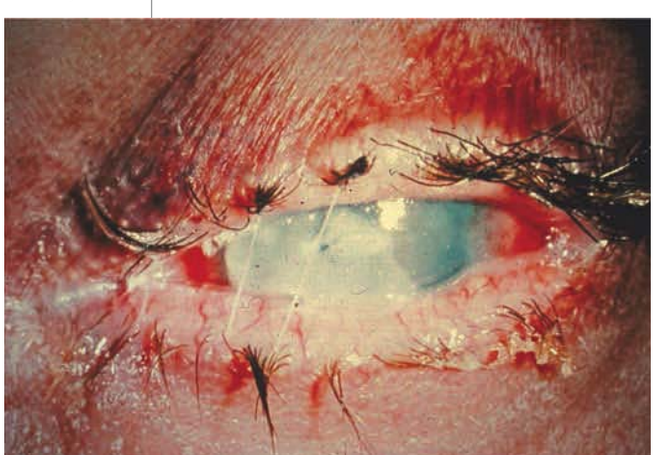
At some national pharmacovigilance centers and some large pharmaceutical companies, the databases holding records of individual case reports of adverse drug reactions are now large, with at least 100,000 or more reports. (Source: McEwen)

Laying Down the Rules

The reports of CIOMS working parties have often then formed the basis for the development of guidelines by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH brings together the regulatory authorities of Europe, Japan and the US, and experts from the pharmaceutical industry in those three regions.

The adoption of ICH guidelines by these three regions, albeit on occasions with some variations between regions, usually results in the documentation and the activities set out in the guidelines being followed by industry worldwide. Europe (combining the resources of the European Medicines Evaluation Agency (EMEA) and the national regulatory agencies) and the US Food and Drug Administration (FDA) have staffing resources with which to implement developments, and such resources are not available at the individual regulatory agencies in Asia Pacific.

At the time of authorization, information on the safety of a medicinal product is relatively limited. Internationally, there has been recognition that the reliance on the duo of analysis of clinical trial safety data prior to registration and case reporting after registration is insufficient to ensure the safety of marketed medicines.



(Source: McEwen)

Particularly driven by initiatives of the US FDA some years ago, attention has turned to the need to monitor the safety of medicines throughout their life cycle and to manage identified real and potential risks. Europe now requires the inclusion of a Risk Management Plan (RMP) in a wide range of registration applications including new active substances, amendments to indications, biosimilar products and some generic medicines. An RMP may also be required if an important safety issue arises during the post-registration (marketing) period.

In summary, the RMP must include a safety specification for identifying known and potential safety issues and missing information about safety. The RMP must justify that routine adverse reaction monitoring will be sufficient, or propose additional pharmacovigilance measures that need to be implemented by the applicant company in the post-marketing period.

The RMP must also justify the product that the usual circumstances of marketing the medicine (usually on prescription) are appropriate to ensure safe use, or propose additional educational activities or access controls. Risk management planning in the US is applied to fewer products than in Europe. When applied in the former country, such planning is currently called a Risk Evaluation and Mitigation Strategy (REMS).

A key outcome of European RMPs and US REMS is that the sponsor company will on occasions commit to undertaking additional pharmacovigilance studies of the newly marketed drug. These can range from intensified case reporting to studies of large numbers of users of the medicine in computerized medical record databases (possible principally in Canada, UK and US) and even to additional blinded, randomized, controlled clinical trials.

Differing Requirements

For the Asia Pacific region, it can be anticipated that some national regulators will require the inclusion of RMPs in registration applications. Australia has implemented this requirement since April 2009. It is probable that regulators in Asia will not often demand additional unique pharmacovigilance commitments, as the needed facilities for most studies, such as large medical record databases, do not yet exist in the region.

More likely, perhaps, is that many regulators in Asia Pacific will demand and to be informed of the commitments for further pharmacovigilance given in Europe and the US and to receive the results of those activities. The European Public Assessment Reports (EPARs) for products approved in the past year, available on the EMEA website, are a source of useful insights into the outcomes of RMPs.

It can be argued that the load on post-registration pharmacovigilance would be reduced through greater attention to the safety of a medicine during its pre-registration development. CIOMS Working Parties VI and VII have considered the management of safety information during clinical trials, and have proposed the implementation of a Development Safety Update Report (DSUR).

Such a report, prepared annually, would summarize for the company, clinical investigators and regulators, the evolving safety profile. The ICH has its final draft guideline (termed E2F) under revision following a period for comment, which is expected to be finalized this year. Once E2F is adopted by ICH, regulators in Asia who authorize or control the clinical trials of new drugs being conducted in their countries can be expected to require the submission of DSURs.

At some national pharmacovigilance centers and some large pharmaceutical companies, the databases holding records of individual case reports of adverse drug reactions are now large, with at least 100,000 or more reports. It is possible to look at the proportion of all reports in the database that are represented by a single adverse reaction descriptor term – for example, hepatitis.

A comparison may then be made of the proportion that the same term makes up for a single drug. A finding that the proportion is higher for the single drug indicates that the reaction is more commonly reported with that drug, and may represent a signal that the drug is a cause of the reaction.

Data Mining

This comparison of proportions is a means of signal generation and, when the process is undertaken repeatedly, may be referred to as "data-mining". Internationally, several methodologies have been developed and their output measures include Proportional Reporting Ratios (UK) and Multi-item Gamma Poisson Shrinker signal scores (US FDA).

Commercial data-mining software is available. None of these output scores confirms a causal role for a drug. Instead, significant scores point to a drug/reaction combination that requires a review of the clinical information.

With the exception of a small number of countries, the databases at national pharmacovigilance centers in the Asia Pacific region are too small to warrant the use of data-mining software. Notwithstanding this, the staff of pharmaceutical companies and regulatory authorities will encounter reports of the outcomes of data-mining and will need to understand their derivation and significance. In this context, the publication by CIOMS Working Group VIII of a report titled "Application of Signal Detection in Pharmacovigilance" is expected and will hopefully be a useful explanatory document.

The increased emphasis by pharmaceutical companies and regulators on pharmacovigilance in Asia Pacific is being accompanied by a need for expert training. An encouraging development is the delivery of training in the region by professional associations and societies. For example, the International Society of Pharmacovigilance (ISoP) presented two parallel training courses in Bangkok in March 2008 with about 100 participants from the region. The society has established a Western Pacific Chapter and is planning for further training in this region in 2010.

"Pharmacovigilance" is a word that was originally used in France in 1972 to describe a national system for the vigilance of the unintended and toxic effects of medicines. It was referred to as "Systeme National de Pharmacovigilance." It is now used in technical English to describe the surveillance, monitoring and investigation of adverse drug reactions. In 2002, the World Health Organization (WHO) published the following definition:

"Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem."

PA

John McEwen is a member of the executive committee of the International Society of Pharmacovigilance and the WHO Expert Advisory Panel on Drug Evaluation.

Drug Delivery

Supply Chain Management: In the Cold

Mechanisms need to be in place to ensure the integrity of temperature sensitive pharmaceutical products in transit. RFID-based monitoring technology may hold the key.

Mayvin Seeneevassen,
Sato

Counterfeiting, diversion and tampering, item-level tagging, and compliance are a few of the challenges that face the pharmaceuticals industry in the management of the supply chain. The industry is increasingly having to comply with regulation and to track their shipments to ensure that the latter have been transported under the correct conditions.

Highly susceptible pharmaceuticals products that must be shipped under a set of prescribed environmental conditions like temperature or humidity, pose another set of challenges. Any supply chain that deals with temperature sensitive material – either perishables or other goods can cause the product specifications to be irremediably altered by temperature. A failure at any point in the cold chain to meet those specifications can lead to losses, product returns, and extra freight costs.

Companies have been experimenting with sensor-equipped Radio Frequency Identification (RFID) equipment and tags to monitor and validate temperature throughout the cold chain. This allows the distributors and the end customer to verify that the products have all been transported under the required environmental conditions. Customer requirements might vary: some can specify that the ambient temperature be the measuring point, whereas others prefer to use the product temperature.

In some cases, the conditions under which the products must be kept are mandated by industry or governmental regulations. Increasingly however, the conditions are determined and enforced internally by pharmaceuticals manufacturers to maintain a high standard of quality and product safety.

Tried, but Still Testing

Aspects of the pharmaceuticals supply chain make virtually any type of track-and-trace solution complex and challenging. Pharmaceutical products use a supply path that is similar to those of other retail products, but drugs typically follow a more disjointed supply chain; they are often sold from one distributor to another to balance stocking levels. Multiple distributors or wholesalers may handle a drug before it finally arrives at a retailer or end user. Barcode-based systems may cost less in the short term, but have demonstrated shortcomings, compared to RFID.

RFID has the capacity to store larger amounts of information, can be read more quickly than barcodes and require less human involvement. Since RFID tags do not require a direct line of sight to be read, they offer the advantage of accurate, mass data capture.

Some major industry players have successfully deployed the technology to manage their supply-chain. In 2007 for example, Pfizer implemented a pilot program by installing tags on all saleable units of Viagra. Other initiatives however, have found it hard to get beyond the concept and trial stages.

Mirroring the challenges faced by suppliers scrambling to meet the compliance requirements of the major retail RFID mandates set by Wal-Mart, Metro and others, pharmaceutical companies face obstacles, some of which are unique to the industry. These challenges include:

- Reading inlays from a distance;
- Reading many closely positioned RFID inlays/labels – in some cases, this could be due to the size of the tagged products, which could range from small vials, to bottles, drums, boxes, cases and other containers (this implies the need for RFID printing equipment that can encode to smaller tags, capable of limiting the antenna coverage area and reducing interference between adjacent inlays/labels);
- Achieving higher read rates through and in liquid environments;
- Achieving higher read rates on tightly packaged products

Enhancing Traceability with Electronic Pedigrees

In 2005, the World Health Organization estimated that more than 10 percent of medicine traded on the global market was fake. In developing countries, 25 percent was counterfeit or substandard. Because of the size of the pharmaceutical market – estimated to be well over US$500 billion worldwide and growing – and because of its cross-border reach, counterfeiting has become a multibillion-dollar problem. It has become a matter of public health and safety with the rising number of cases of people falling sick or worse after taking pharmaceutical products of suspicious origin.

The US Food and Drug Administration (FDA) stated as early as 2004 that RFID represents an important tool to help improve the safety of the drug supply chain. There have been various meetings to encourage industry players to collaborate in a pilot track-and-trace program based on RFID and related technologies such as mass serialization and electronic drug pedigrees. The idea was to have a system in place by the end of 2007. However, this has not materialized yet.

The initiative of the California Board of Pharmacy to combat counterfeit drugs by requiring an electronic pedigree on drugs was meant to spur the industry to develop standards for serialization. The proposal, originally set for implementation in 2007 in line with the federal goal, even warned retail pharmacies that they might not be able to receive drug shipments if the drugs did not carry electronic pedigrees from manufacturers.

However, delays in the system's deployment have caused the implementation date for manufacturers to be pushed back to 2015, and an even later date for retailers. The FDA on the other hand has issued draft rules on tracking drug shipments through the system, with its 2008 proposal, "Standardized Numerical Identification for Prescription Drug Packages."

Stronger requirements to safeguard the drug supply chain are on the way, including specific requirements for the cold chain. Many countries are pushing for legislation that will provide the oversight of pharmaceutical product tracking and tracing through the accumulation of a product pedigree, which details specifics about the supply chain history of each drug shipment.

Industry associations such as the US Healthcare Distribution Management Association (HDMA) are also promoting the accelerated adoption of electronic track and trace using Electronic Product Code (EPC) tagging. Plans are to target adoption at the case level initially and progress to individual selling units at a later stage as the system gains acceptance. At the same time, RFID standards groups such as EPCglobal are exploring the standards and practices that need to be established to adopt electronic track-and-trace technologies throughout the supply chain.

Keeping it Fresh

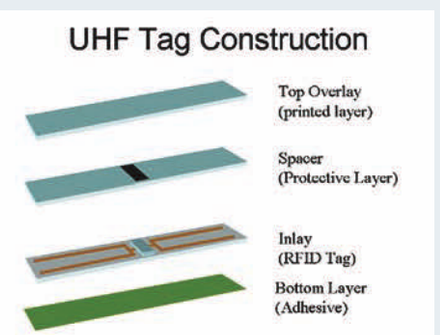
Perishable pharmaceutical products have a shelf life that is determined not only by time, but also by the temperature and other conditions in which they are stored. Retailers often have to use the FEFO (First Expire, First Out) concept to manage products that might have different shelf lives. Temperature variations can occur at various points in the cold chain, such as in warehousing, handling and transportation. A study by Deloitte discovered that "microclimates"

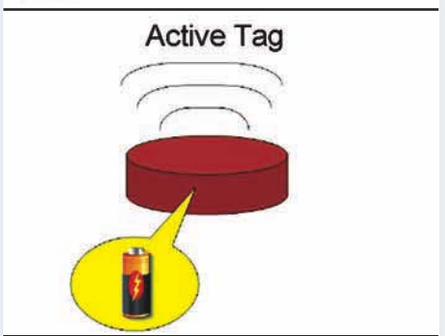
RFID: A Primer

The RFID tag/inlay is basically a programmable tool consisting of an RFID chip for data storage. RFID tags are categorized as either passive or active. Passive tags do not have an integrated power source and are powered from the signal carried by the reader. Active tags have a built-in power source, and their behavior can be compared to that of a beacon. As a result of the built-in battery, active tags can operate at a greater distance and at higher data rates in return for limited life – driven by the longevity of the built-in battery.

Due to a lower cost of implementation, passive tags are a more attractive solution for some businesses.

The other component of the system is the reader system that serves to interrogate the tag and facilitate communication with the RFID chip.





(Source: Sato)

Drug Delivery

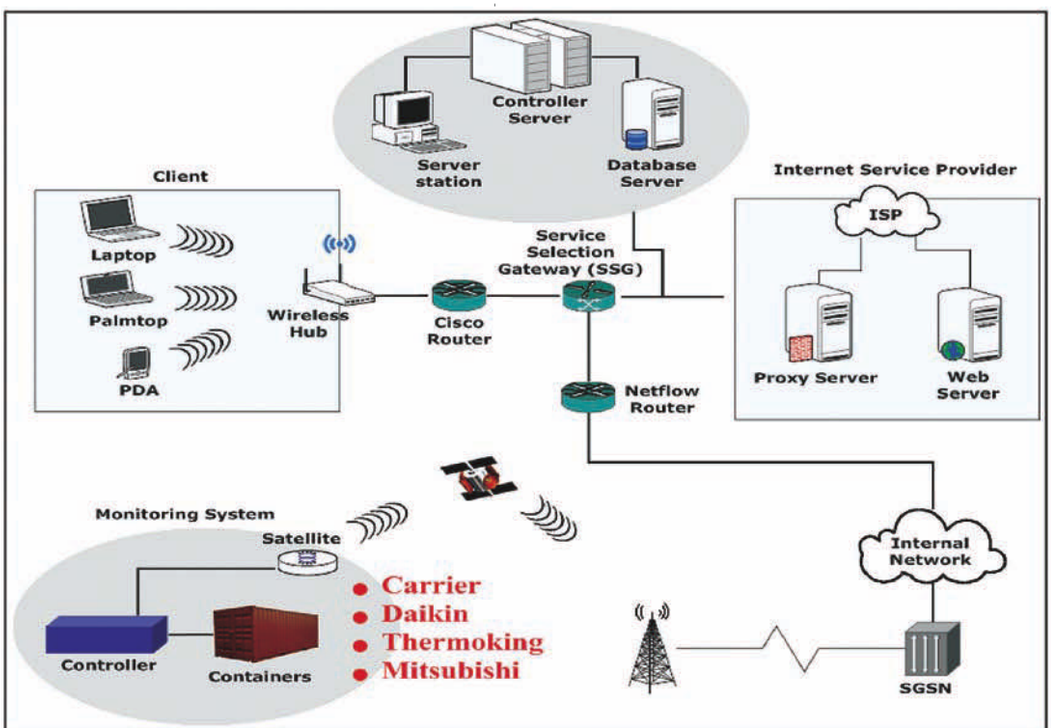


Illustration of Remote Reefer Monitoring (Source: Sato)

not only occurred between the front and back of a refrigerated trailer but also within stacks of pallets. Results were somewhat surprising. In one test, the bottom pallets in the middle of the trailer experienced a nearly seven degree temperature variation.

The study used temperature-logging RFID tags on pallets in both static and moving refrigerated trailers. It is a solution that has received some traction with those involved in the pharma cold supply chain. Companies are considering using temperature-logging sensor-equipped RFID tags that can help to reduce waste in the perishable pharmaceuticals supply chain. Temperature is not the only issue though; humidity and shock can also play a role in affecting product shelf-life. Some sensors can detect all of these conditions and more.

As companies acknowledge that RFID can help to eliminate waste in the cold chain, there is likely to be greater collaborative efforts to take advantage of these tools to improve performance and profit.

RFID technology is said to have improved the performance of the total supply chain in two key areas. Firstly, it can be used as a way to trace the geographical location of the individual cargo, container or truck, which can either be stationary or in motion. Sensors are installed at strategically located doors and gantries to track the movement of the container. Information on the container such as date, time, location, and cargo number is picked up by the sensors at the gantry and is reflected in the central system or a mobile computer located in the proximity.

This method also enables containers to be tracked twenty-four hours a day. It is particularly helpful for companies that need their shipments to arrive at the desired destination by a specific date and time. If the shipment is delayed, information can be retrieved from the system to enable specific measures to be taken to speed up the delivery process.

Secondly, RFID technology is used to identify each item with a unique EPC. This is particularly useful for tracking specific items that require real-time data such as temperature. These data are then transmitted in real-time to another location where critical decisions (such as product recalls) can be made.

Savings and efficiency gains can be realized once an RFID system is in place. For example, the costs savings from tracking and reusing tagged shipping containers.

Up and Coming Technology

Containers that have been returned are inspected for their internal conditions before reusing. If the seal or lock is not broken and where no other visible damage on the outer container is detected, it is generally assumed that tampering has not taken place.

However, a more effective method is to perform checks at strategic points of transit to detect any damaged or tampered containers. The way to go about this is to enable battery-powered container units which are connected to the internet, and to monitor them real-time via a RFID-enabled system.

This type of usage is common for keeping track of cold chain applications, for example, the monitoring of refrigerated containers or reefers.

The RFID system for reefer monitoring is designed to provide companies with end-to-end visibility into their cold chains – and to alert cold chain partners if the cargo is at risk of falling outside the acceptable temperature range. Custom-made devices are built into active RFID transponders that are placed inside pallets or containers before putting the latter into transit.

The sensors record and store information such as temperature and humidity. The information is transmitted via the tags to readers that are installed in the control center. The data is collected and shared centrally to allow all supply chain users to receive the same information simultaneously in real-time.

There are niche solutions that cater to this type of requirement. One of them is the Reefer Monitoring and Alert System (ReeMAS: Patent Pending Technology – PCT/SG2008/000261) that enables shippers, reefer owners, freight agents, shipping lines, port operators, and consumers to remotely monitor the reefer's status via the internet. This non-intrusive system is capable of providing the monitoring of reefer containers onboard a land transport vehicle, vessel or in a container terminal.

This methodology allows the extraction of critical data remotely. If any discrepancies are detected, alarms will be activated by the reefer containers. On-site operators will be notified at the same time for immediate remedial action and the alerts can be communicated to the central operations via email or sms.

This system makes use of wired and wireless Mesh technology and/or satellite communication to provide remote monitoring capabilities with minimum setup effort. The acceptable temperature and humidity levels are set and form the benchmark. Examples of tracked information include:

- Date taken
- Time taken
- Set temperature level
- Return air temperature
- Supply air temperature
- Set humidity level
- Humidity level
- USDA sensors
- Reefer's alarms

Physical Device on Reefer (Source: Sato)

This cold chain end-to-end reefer monitoring system can operate in standalone or networked mode, linking the entire supply chain's users from land and sea, and from fixed or moving locations.

Be Armed, Not Alarmed

Setting up a tracking facility surrounding container monitoring and control is not difficult provided that the key stakeholders recognize the key control points, key information to track, and the results of such controls.

When considering the purchase of a cargo security device or container traceability system, considerations include the provider's expertise in accurate data capture and transfer, identification and tracking as well as meeting related requirements in challenging environments.

It may also be necessary to determine if the provider supplies hardware such as printers and scanners, and software such as label creation. **PA**

Enquiry code: 096E08

Advancements in Capsule Inspection Technology

Inspection systems are now capable of detecting a wider range of defects, in capsules that vary in size and color combination.

Angela Dove,
writer

Consumer demand for hard shell capsules as the preferred delivery mode for pharmaceuticals is also driving the development of alternatives to hard-gel (shells that are derived from gelatin) capsules. However, the different characteristics of these next generation capsules pose a different set of challenges for pharmaceutical manufacturers in terms of visual quality inspections – challenges that visual inspection systems are now equipped to deal with, to ensure quality and safety compliance no matter which type of gel capsule is used.

Problem Resolution

Inspection systems have been developed that can perform the visual inspection of the different types of capsules that are available on the market today. The machines are equipped with generic format parts – this means that the operator can perform a quick change of machine parts when there is a need to process capsules of a different size.

The inclusion of this feature allows one system to check different types of capsules with just a quick adjustment to the settings. Such a capability, coupled with high-speed sorting and easy cleaning, helps to achieve lower downtime and enable higher efficiency.

Due to their intrinsic properties, capsules tend to generate static electricity. This causes the capsules to bunch together, presenting the potential to foul up the sorting line. To solve this problem, some systems come equipped with a de-ionizer that removes static electricity from capsules via a contactless "pass-over" method. In order to further upkeep a smooth operation, vacuum suction is also used on the conveyor belt to keep capsules lying flat and in place for optimal inspection.

Inspection systems have been developed that can perform the visual inspection of the different types of capsules that are available on the market today. (Source: Proditec)

In the past, visual inspection technology was not able to adequately inspect the hemispherical tips of capsules, as their curvature required different inspection settings. The different color combinations of the two capsule halves also used to pose inspection challenges, as each color requires a different amount of light to allow for adequate inspection.

This physical characteristic of hard gel capsules interfered with, and in some cases prevented an accurate check for defects. However, with the technology available today, the inspection of hemispherical capsule tips and duotone capsule components is no longer a challenge.

Improvements in lighting systems and image processing software that are used in such machines have resulted in the ability to check even translucent capsules for defects such as errors in printing, chipping, notching, double-capping and telescoping.

Content and Filling Inspection

Consequently in addition to the detection of external flaws, the quantity of content and filling in translucent capsules can also be inspected, fulfilling a critical requirement of pharmaceutical suppliers.

An important defect that is found at the final inspection stage is that of capsules which contain holes that are microscopic in size, but can admit contaminated air. This flaw also allows the contents to leak out, creating issues with accurate dosing. Visual inspection technology today is able to accurately detect these defects, adding yet another layer of protection.

Another feature of certain machines is the ability to inspect radial or longitudinal printing on each capsule without the need to rotate the latter. This is possible because one dedicated set of cameras and mirror systems can capture four separate views of the capsule.

These views are then "stitched" together to create a flat view of the full body, making the capsule easier to inspect and match against the "master" pattern that has been taught to the program. This full-panoramic view inspection is accomplished at a high speed; up to 120,000 capsules per hour can be inspected. Any printing discrepancies that are detected on a capsule will automatically cause it to be ejected.

With these advancements and features, the latest generation of capsule inspection machines offer comprehensive and thorough inspection that improves safety and quality. High-speed sorting capabilities and quick part changes reduce downtime and increase productivity.

In order to meet the needs of Asia's growing pharmaceutical market, the Human Machine Interface (HMI) is available in all major Asian languages along with English – a feature that helps to support full 21 CFR Part 11 compliance and its associated audit trail reports.

Demand for Variety

Hard gel capsules are versatile – being available in a number of sizes ranging from 00 to 5, making them suitable containers for a variety of drugs.

Such capsules are also favored because their range of color combinations serves as an easy way for consumers to recognize and differentiate between multiple medicines. They are also more easily swallowed than softgels or tablets. By being easy to identify, remember and consume, hard gel capsules help consumers achieve and maintain an enhanced level of patient compliance.

Many health-conscious consumers who take health and beauty supplements are also starting to avoid sugars, starches and animal-derived ingredients in hard gel capsules that are made of gelatin, in favor of other alternatives. Religious beliefs and a growing vegetarianism movement, too, contribute to the desire for hard gel capsules that do not contain animal derivatives.

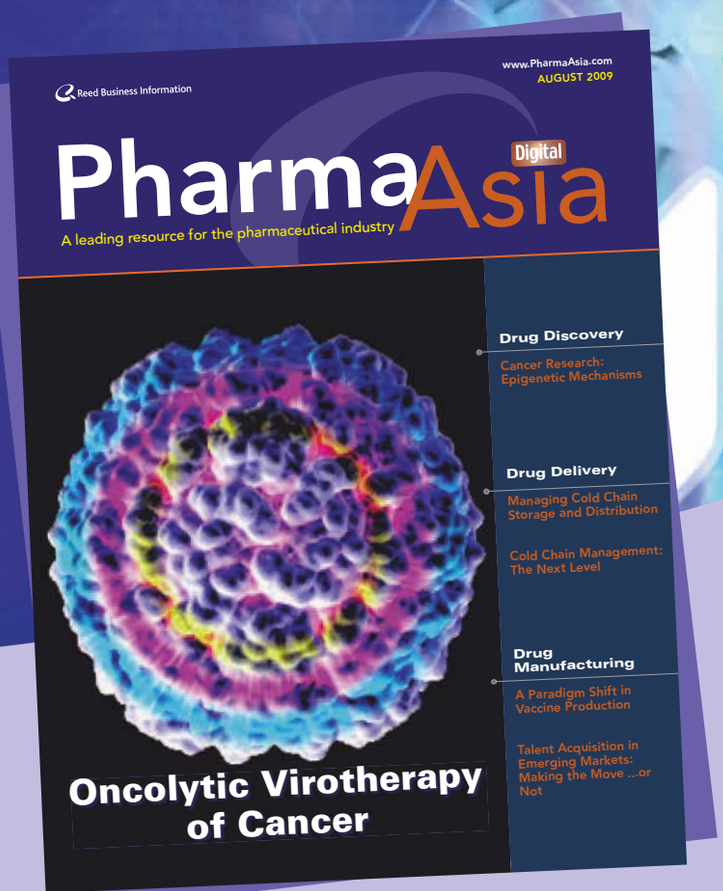
These changes in consumer demands have spurred the creation of capsules that are made from other materials such as seaweed and starch, as well as innovative chemical compounds like Hydroxypropyl Methyl Cellulose (HPMC). The general increase in market demand has also given rise to more capsule manufacturers in the industry. With the variety of capsule types that are now available on the market, capsule manufacturers and pharmaceutical companies must face increased challenges in ensuring safety and quality standards. **PA**

Enquiry code: 096E09

With these advancements and features, the latest generation of capsule inspection machines offer comprehensive and thorough inspection that improves safety and quality. High-speed sorting capabilities and quick part changes reduce downtime and increase productivity.

Reach Out!

Aiming to make your presence known in Asia? Launching a new product or service?



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Product Focus
Test/Measurement

Laser Sizer for Particle-Sized Measurements

The Analysette 22 MicroTec Plus lazer particle sizer from Fritsch is used for particle-sized measurements. It utilizes dual-laser-technology and comes with a Fast-Switch-System. This means that the measuring cells of the system are located in cartridges, which are simply exchanged during the switch from wet to dry measurements – and can be performed without tools. The cartridge can be stored in the corresponding dispersion unit when it is not in use.

Users can choose between two individual measuring ranges or combine both into a third range. This results in an overall measuring range from 0.08 µm – 2000 µm with a resolution of up to 108 measuring channels.

The wet dispersion unit is equipped with a centrifugal pump for the optimal transport of even heavy particles with a high concentration, through the measurement system. With the help of an intelligent liquid-level-sensor, three individual amounts of liquids can be set by default. The use of common organic solvents as suspension liquids is possible.

A variable ultrasonic-system linked to software manages complex measurement sequences that are fully automatic and reproducible.

Fritsch, www.fritsch-laser.com

Enquiry code: 096P01

Direct Reading Rotameters

Aalborg Instruments has introduced the Model xV multi-gas glass tube flow meters. These units feature rotatable scale drums for displaying the flow rates of five routine gases (argon, carbon dioxide, helium, nitrogen, and oxygen).

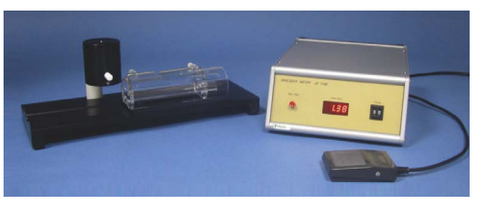
The multi-gas rotameters eliminate the need for individual flow meters and calibrations. Easy-to-read direct reading gradations showing dual Standard Cubic Feet per Minute (SCFM) and L/min markings, reflect both metric and English systems.

The heavy-walled, fluted borosilicate glass flow tubes with polycarbonate shields are assembled in brass or 316 stainless steel frames. The rugged meters offer accurate, economical solutions to medium flow range measurements. Vertical in-line or panel mount models are available.

Aalborg, www.Aalborg.com

Enquiry code: 096P02

Tail Flick Meter for Evaluating Thermal Analgesia



Harvard Apparatus has introduced the Tail Flick analgesia meter for studying the analgesic properties of pharmacological substances in rats or mice. The system supplies radiant heat on the animal's tail and measures the duration to a response – the tail flick.

This analgesia meter achieves the optimal detection of the tail flick by ensuring the correct placement of the animal's tail and aligning the heat stimulus and the photo-beam trigger.

Start/stop is controlled either from the front panel or footswitch, and the automatic safety shut-off makes this a simple, user-friendly system. The analgesia meter is supplied with SeDaCom Software for automatically recording results on a PC.

Harvard Apparatus, www.harvardapparatus.com

Enquiry code: 096P03

Union Biometrica: Cytometers for Large Particles

Union Biometrica has introduced the Copas Large Particle Flow cytometers. These instruments can analyze, sort and dispense objects that are too large (20-1,500 micron) or too delicate for traditional flow cytometers.

Typical samples range from small multicellular model organisms (C.elegans, D.melanogaster, Zebrafish) to delicate large cells / cell clusters (adipocytes, embryoid bodies, pancreatic islets, duct cells, hepatocytes), to seeds (Arabidopsis) and beads (cells growing in or on beads, combi-chem libraries, bead based assays).

Samples are analyzed one by one in a continuously flowing stream and each object is analyzed and sorted based on size, optical density and up to three fluorescent parameters.

Examples of applications include rapid dispensing into micro-titer plates for assay preparation, population enrichment prior to further experiments, isolation of rare events, and the quantification of fluorescence levels of each object.

Union Biometrica, www.unionbio.com

Enquiry code: 096P04

Calendar of Events

Sep 7 – 9, 2009
BioProcess International China 2009
Beijing, China
www.ibclifesciences.com/BPIChina

Sep 13 – 15, 2009
ISPE Australasia Conference 2009
Sydney, Australia
www.ispe2009.com

Sep 14 – 15, 2009
Thermo Fisher Scientific – Spectroscopy User Meeting
Stratford, UK
www.thermo.com/ukscievents

Sep 16 – 18, 2009
Bio Korea 2009
Seoul, South Korea
www.biokorea.org/info/bio_korea_01.html

Sep 16 – 18, 2009
World Pharmaceutical (China) Summit 2009
Shanghai, China
www.cfeci.com/wpcs2009

Sep 22 – 23, 2009
In-Vitro Diagnostics Technologly Congress
Marriott Hotel Hongqiao,
Shanghai, China
www.ivdtechcongress.com

Sep 23 – 25, 2009
World Pharma Trials Asia 2009
Shanghai, China
www.terrapinn.com/2009/pharmatrials

Sep 24 -25, 2009
Medical Devices Summit 2009
Shanghai, China
www.ibc-asia.com/medicaldevices

Oct 5 – 7, 2009
Stem Cells & Regenerative Medicines Asia 2009
Singapore
www.terrapinn.com/2009/stemcellsasia/

Oct 6 – 8, 2009
Biotechnica
Hannover, Germany
www.biotechnica.de

Oct 8, 2009
Clinical Outsourcing Alliances in India
Boston, Massachusetts, USA
https://www.nextlevelpharma.com/events/view/clinical_outsourcing_alliances_india

Oct 16, 2009
RNAi Market Analysis and Business Tutorial
Kunshan/Shanghai, China
www.selectbiosciences.com/conferences/RazviLondon/RNAi_Tutorial.aspx

Oct 19, 2009
Stem Cells in Drug Discovery and Regenerative Medicine
Tokyo, Japan
www.selectbiosciences.com/conferences/Razvi_19OCTpm/

Oct 19 – 20, 2009
Wyatt Technology Corporation - 20th Annual International Light Scattering Colloquium
California, US
www.wyatt.com/events/colloquium/

Oct 20, 2009
MicroRNA and Epigenetics
Tokyo, Japan
www.selectbiosciences.com/conferences/Razvi_20OCTam/?utm_source=SBTrngJune09

Oct 20, 2009
Nucleic Acid Diagnostics and Therapeutics
Tokyo, Japan
www.selectbiosciences.com/conferences/Razvi_20OCTpm/?utm_source=SBTrngJune09

Oct 22 – 25, 2009
BIT's 7th Annual Congress of International Drug Discovery Science and Technology (IDDST)
Shanghai, China
www.iddst.com

Nov 1 – 3, 2009
HUGO Symposium on Genomics and Ethics, Law and Society
Geneva, Switzerland
www.hugoevents.org/gels/

Nov 8 – 10, 2009
ChinaTrials 2009
Beijing, China
www.chinatrialsevent.com/agenda.php
www.en.newdrugschina.com

Nov 11-13, 2009
Interphex China
Beijing , China
http://en.interphexchina.com

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