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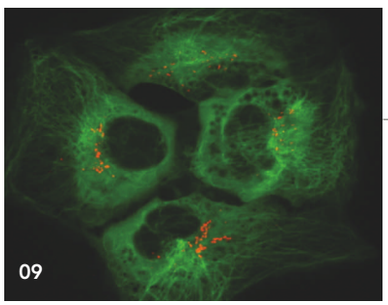
Contents



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Editor's Note

Michael Tham
Editor

Asian Attraction

It seems that pharmaceutical companies are continuing to expand eastward. More are moving in to capitalize on the benefits offered by Asia's pharmaceuticals industry. PerkinElmer for one, has opened a training academy and a logistics center in Mumbai, India – not long after inaugurating a research facility in Singapore earlier in the year.

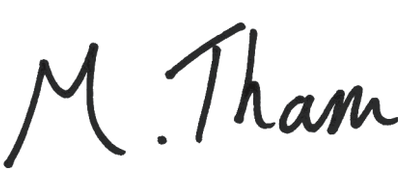
Finnish company Orion has inked a deal with India-based Jubilant Organosys, allowing the former to utilize resources from the latter's subsidiaries in India for drug discovery projects.

The availability of talent, a flexible resource supply and cost-effectiveness are just some of the pull-factors for Western companies that need to reduce their cost structures. For example, outsourcing R&D to China can help companies to achieve a saving of 60 to 70 percent, according to a report by JZMed (page 14).

For some, cross-border cooperation has proven to be a fruitful experience, enough for both parties to extend collaborative agreements into the immediate future and beyond (page 8). Chinese Contract Research Organization (CRO) BioDuro has announced a partnership to support discovery phase research efforts at Roche.

The alliance between GVK Biosciences and Excel PharmaStudies (page 8) adds an interesting twist that helps the two companies to leverage upon each other's strengths – besides allowing both to gain from the unique benefits offered by China and India – for the various stages of drug development.

Yet, the expansion of Asia's pharmaceutical industry is not without its challenges. In our three-part series beginning this issue (page 18), the report by Sharpstream Life Sciences describes a situation where the supply of labor is having problems in keeping up with demand. This makes it important for top management to correctly understand and to meet the needs of their staff – in order to continue to attract, motivate and retain them. **PA**



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Tuberculosis in Developing Countries

Despite being a global disease, the burden of tuberculosis (TB) is most severe in developing countries, particularly those in Asia and Africa, according to Datamonitor. Despite the fact that TB is almost endemic in some regions, case detection rates remain very low, which poses a significant obstacle for its control. Although the key unmet need in the developing world is a vaccine that targets the pulmonary instance of the disease, new antibiotics may hold significant potential. The World Health Organization estimates that in 2006 there were 14.4 million prevalent cases of TB, 9.2 million new cases and 1.7 million deaths from TB globally.

TB is a burden in developing countries, with Asia (South-East Asia and Western Pacific regions) and Africa accounting for 55 percent and 31 percent respectively, of global cases in 2006. Although the occurrence of TB in the seven major markets (7MM – ie, US, Japan, Germany, France, UK, Italy and Spain) has declined sharply over the last few decades, deteriorating socioeconomic circumstances and the impact of HIV/AIDS have exacerbated the TB epidemic in the developing world (in 2006, 700,000 cases and 200,000 deaths occurred in people who were HIV positive). Furthermore, effective case detection in these regions is impeded by the lack of rapid and inexpensive diagnostics, which poses a significant obstacle to TB control.

Public-Private Partnerships Drive Search for Novel TB Vaccines

Experts agree that the introduction of an efficacious TB vaccine holds the greatest promise for achieving TB control. There are several drawbacks to the only currently available vaccine, bacillus Calmette-Guerin (BCG). This live vaccine protects against severe childhood forms of disease, including milliary and extrapulmonary TB and the often fatal TB meningitis. However, it does not prevent the establishment of primary infection or reactivation of latent TB, with the latter condition being the main source of mycobacterial spread in the community.

As a consequence, a vaccine which targets pulmonary TB represents the single most important unmet need in TB, particularly in the developing world, according to Datamonitor infectious diseases analyst Richard Phelps. "Given that there is currently no biomarker of treatment response for TB, there is also a large unmet need for rapid and inexpensive diagnostics. These could reduce the length of clinical trials and improve the ability to assess the efficacy of vaccines."

Vaccine development for TB has been hampered by a number of challenges. These include safety issues, particularly in the HIV-infected population, large and lengthy clinical efficacy trials, the selection of appropriate immunization strategies, and the identification of the most suitable type of vaccine.

The decline in TB incidence in the developed world has reduced the commercial attractiveness of the market for pharmaceutical companies. This has resulted in a lack of industry investment in anti-tuberculosis research and a dearth of new drugs and vaccine candidates.

After a period of inactivity, a number of vaccines for TB have reached clinical stages of development, with public-private partnerships being a key driver. The Aeras Global TB Vaccine Foundation, which receives funding from a number of donors such as the Bill and Melinda Gates Foundation, is currently working on six candidate vaccines. The foundation is developing these through collaborations with companies like Crucell, GlaxoSmithKline and Sanofi Pasteur.

Several vaccines and strategies are being investigated for both the prevention and the treatment of TB, addressing the limitations of the current BCG vaccination. Approaches that are currently being investigated include the replacement of the BCG with a more efficacious vaccine, boosters for BCG vaccinated adolescents/adults which prevent adult pulmonary TB and immunotherapeutic vaccines.

The vaccine candidates include BCG strains that have been genetically manipulated to express immunodominant antigens (recombinant BCG) and several non-living vaccines (ie, subunit; DNA; and viral vector vaccines).

Improved Therapy Options

Another approach for TB control is the treatment of infected patients. In 2007, the global TB antibiotics market was worth approximately US$300 million with a compound annual growth rate of 2.2 percent from 2004-2007, according to IMS Health. Given the low incidence of TB in the 7MM, these accounted for only about 40 percent of total sales, while the balance was accounted for by the rest of world. India alone represents approximately 23 percent of the world market.

Antituberculosis drugs have traditionally been classified into first and second-line drugs for antibiotic susceptible and resistant TB strains, respectively. The most frequently recommended and effective combination consists of isoniazid, rifampicin, pyrazinamide and ethambutol for two months followed by isoniazid and rifampicin for four months. However the long duration of therapy and side effects associated with the respective drugs can lead to non-adherence, which in turn can cause treatment failure and bacterial resistance.

Second-line therapy is prescribed following failure or resistance to initial regimens. It currently represents the area with the greatest commercial opportunity since many second-line drugs have greater toxicity. In the case of extensively drug resistant tuberculosis, they are simply ineffective.

Candidates currently being investigated include the fluoroquinolones gatifloxacin and moxifloxacin, Tibotec/Johnson & Johnson's TMC207, Chiron Pathogenesis/TB Alliance's PA824, Otsuka Pharmaceuticals' OPC-67683 and Sequella's SQ-109. While the fluoroquinolones may be able to shorten the duration of therapy for drug susceptible tuberculosis, their activity will be limited against extensively drug resistant strains.

More promising are the drugs with a novel mechanism of action such as the ATP synthase inhibitor TMC207, given their activity against highly resistant strains. Phelps says, "newer drugs which can substantially reduce the duration of therapy and have activity against MDR- and XDR-TB strains have a strong chance of achieving commercial success." **PA**

Celtic Pharma Announces Successful Phase II Trial For Onychomycosis

Celtic Pharmaceutical Holdings has announced the successful outcome of its Phase II trial of TDT-067, terbinafine in Transfersomes, for the treatment of onychomycosis.

The clinical trial treated patients for 12 weeks with a primary endpoint of mycological cure at 14 weeks and follow-up to 48 weeks. A 90 percent negative mycological cure rate was observed at 14 weeks. At 48 weeks the mycological cure rate was still 38 percent despite no active treatment for the preceding 36 weeks. TDT-067 was well tolerated with negligible systemic drug exposure (no patient had more than 2ng/ml of terbinafine at steady state and the large majority of the patients had no detectable levels, ie, below 1 ng/ml).

The trial explored the efficacy and safety of topically applied terbinafine delivered through the Transfersome targeted delivery technology. **PA**

Elan and Wyeth to Amend Bapineuzumab Phase III Protocols

Elan Corporation and Wyeth will discontinue the highest of three dosing regimens, 2.0 mg/kg, in the two ongoing Phase III studies of bapineuzumab in patients with mild to moderate Alzheimer's disease (AD) who do not carry the Apolipoprotein E4 (ApoE4) allele (non-carriers). The 0.5 mg/kg and 1.0 mg/kg doses in these two trials will continue as planned.

This decision has no impact on two other ongoing studies, which are testing a single 0.5 mg/kg dose of bapineuzumab in patients who carry the ApoE4 allele (carriers). No changes are planned for these two carrier studies. It is expected that approximately 4,000 patients will be included across all four studies.

The decision of the companies to discontinue the 2.0 mg/kg dose was made in concurrence with the study's independent Safety Monitoring Committee (SMC), following its review of vasogenic edema (VE) in the ongoing Phase III clinical program.

Newly enrolled patients will be randomized to either the 0.5 mg/kg or the 1.0 mg/kg dose cohorts or to placebo. The companies plan to amend the protocols to allow patients who are currently receiving the 2.0 mg/kg dose to be reassigned to the 1.0 mg/kg dose.

The companies' decision to modify the dosing regimen for two of the four ongoing Phase 3 studies is being communicated to study investigators and the Boards of Health where the clinical trials are being conducted. **PA**

HRA Pharma Receives Positive Opinion for Contraceptive Drug

HRA Pharma has announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) has issued a positive opinion recommending a marketing authorization for ellaOne (ulipristal acetate), an emergency contraceptive.

The commission is reviewing the CHMP final opinion in order to grant a community marketing authorization, which will be valid throughout the European Union. Once formally approved, ellaOne will be the first product to have been specifically designed and developed for use as an emergency contraceptive, according to the company. The drug has improved clinical characteristics over existing hormonal treatments: a good safety and tolerability profile and the advantage of sustained efficacy up to five days following unprotected intercourse or contraception failure.

HRA Pharma expects to file for marketing approvals in countries worldwide under the trademarks ellaOne and ella. **PA**

Acacia Pharma: Phase IIa Study for Cancer Cachexia

Acacia Pharma has initiated a Phase IIa study of its product APD209 to treat cachexia in cancer patients. The drug has been designed to target specific problems experienced by cachectic patients, in particular, inadequate nutrition and active muscle breakdown.

Cachexia is thought to be the direct cause of death in around 20 percent of advanced cancer patients. However, there is no generally approved or accepted therapy.

Professor Kenneth Fearon, the Professor of Surgical Oncology will conduct the study at the Royal Infirmary, Edinburgh, UK. The plan is to treat up to 16 patients for eight weeks with APD209 and to take measurements of muscle size, muscle function, overall activity, quality of life and other parameters to assess the efficacy of the product. Safety and pharmacokinetics will also be evaluated. The trial is expected to last for nine months and initial read-out is anticipated in fourth quarter 2009. **PA**

Drug Helps Patients to Quit Smoking

Pfizer has announced the results of a study that found that 47 percent of smokers with a history of cardiovascular disease who took Champix (varenicline) – also known as Chantix in the US – were able to quit smoking and remain abstinent during the last four weeks of treatment (weeks 9-12) compared with just 13.9 percent of those given placebo

"These data are consistent with the findings from the pivotal varenicline trials, which showed that varenicline was more effective than placebo among smokers who were generally healthy," said Dr Nancy Rigotti, professor of medicine at Harvard Medical School, director of the Tobacco Research and Treatment Center at Massachusetts General Hospital, and lead study investigator. "This study demonstrates that it is effective in helping smokers with cardiovascular disease to quit smoking. The safety profile of the drug in this study also resembles that of the pivotal studies. The results are encouraging because the participants were at greater risk for death given their advanced ages, durations of smoking and histories of cardiovascular disease."

The multicenter, double-blind, placebo-controlled trial included 714 adult patients (ages 35-75 years) who had smoked an average of 10 or more cigarettes daily in the year before enrollment. All patients wanted to quit smoking but had not tried to in the past three months, and had stable, documented cardiovascular disease that had been diagnosed more than two months prior. Eligible cardiovascular disease diagnoses included history of heart attack, a certain type of heart surgery, chest pain, peripheral arterial vascular disease, and stroke or transient ischemic attack.

At the end of 52 weeks, 19.2 percent of patients who were randomized to take varenicline during the treatment phase remained abstinent, compared with 7.2 percent of patients randomized to take placebo. The trial was conducted in 15 countries. **PA**

Source: Karol Stróż

SAFC Expands CHO Portfolio

SAFC Biosciences has expanded its portfolio of products and services for use in Chinese Hamster Ovary (CHO) cell line applications. The company has introduced the Ex-Cell CD CHO Fusion and the CHO cGMP Media Library, a media screening library of formulations.

The CHO Fusion media has been developed to work as a scalable platform media formulation. This is for cell culture applications that require a chemically defined animal-component free media option that can meet production requirements across multiple CHO cell lines.

According to Mason Williams, Product Manager, the company is already seeing the early adoption of this formulation by companies in the biopharmaceutical industry as a result of their participation in a beta-site testing program. "One early customer," says Williams, "has already requested larger quantities for projects in clinical process scale-up."

According to Archie Cullen, VP of Global Commercial and Technical Operations, "We have developed a program that we believe allows clients to screen a robust offering of media formulations through the CHO Library to identify the best starting point for every application. The program also reduces concerns around scale-up by having the formulations already produced to Current Good Manufacturing Practice (cGMP). The next step in this approach is the launch of a Platform Chemically Defined Supplement that effectively removes the dependence on hydrolysates or other undefined components that have challenged production processes." **PA**

Regenerative Medicine Offers Hope for Incurable Diseases

Stem cell therapies could replace diseased body tissue, offering hope for patients with incurable conditions such as Parkinson's disease and diabetes.

At the 35th Annual Meeting of the European Group for Blood and Marrow Transplantation (EBMT), Prof Katarina Le Blanc (Karolinska Institute, Stockholm, Sweden) chaired a session in which researchers discussed how stem cell therapy could regenerate other body tissue, thereby improving human health and the quality of life.

Regenerative medicine aims to treat currently incurable disorders, including neurodegenerative diseases such as Parkinson's disease, affecting around 6.3 million people worldwide. It may also be used to treat muscular dystrophy and multiple sclerosis, and to repair or replace nerve cells (or "neurons") damaged by spinal cord injury.

Regenerative medicine also has potential to generate new insulin-producing cells in people with diabetes. Other uses include the growth of new cardiac muscle cells for patients who have suffered from heart attacks. Stem cell therapy may either work by providing new stem cells to the patient or by stimulating growth of the patient's own stem cells. Scientists have learned about how stem cells contribute to the regeneration of tissue in the human body after birth.

Dr Kirsty Spalding and co-workers (Karolinska Institute, Stockholm, Sweden) aged brain neurons by measuring levels of radioactive carbon-14, generated by nuclear bomb tests during the Cold War, in people's DNA. Neurons in the brain's cerebral neocortex are as old as the individual, ie, these cells are only generated around the time of birth and not in adulthood. This means that the body cannot normally replace these cells if they are damaged or diseased.

Bone marrow 'stromal' stem cells are able to differentiate into various types of tissue that form the skeleton, including bone and cartilage. Prof Paolo Bianco ("La Sapienza" University, Rome, Italy) and co-workers have shown that stromal cells may be used to reconstruct bone, for example in the reconstruction of the face in with patients with injuries.

Experiments conducted by Prof Yair Reisner and co-workers (Weizmann Institute, Rehovot, Israel) suggest that in the future it may be possible to grow organs such as the liver by transplanting stem cells from one individual to another. **PA**

BioSingapore Recognizes Biotech Companies in Asia Pacific

BioSingapore has announced the five most innovative and successful companies in the biotechnology field in Asia Pacific, as well as the Woman Entrepreneur of the year.

"The BioSingapore Awards 2009 exemplify the growing economic impact and success of the biomedical industry, not only here in Singapore but throughout the Asia-Pacific region, and the importance of the close collaboration between the regional biotechnology organizations working together in the BioNetwork Asia-Pacific (BNAP)," said Prof Sir David Lane, chairman, Biomedical Research Council (BMRC), Singapore.

The event was attended by life science conference participants and exhibitors from around the world, as well as by scientific and industry leaders, research institutions, and Singapore government officials.

There are six categories for the awards. The 2009 winners are:

1. Most Innovative Start-Up – Siogen Biotech, Malaysia
2. Best Listed Company – Biocon Limited, India
3. Most Successful Bio-Partnership – S*BIO Private, Singapore
4. Most Important Technology Development – XCyton Diagnostics, India
5. Best Performing CRO – Parexel Apex International, Taiwan
6. Woman Entrepreneur of the Year – Dr Deborah Rathjen, Bionomics, Australia

The judging panel consisted of Dr Anna Lavelle, CEO and executive director, AusBiotech; Dr Shrikumar Suryanarayan, director general, Association of Biotechnology-Led Enterprises of India; Dr Jonghoon Choi, secretary general, Korea Biotechnology Industry Organisation; and Dr Michael Entzeroth

Siogen

Siogen Biotech

Equipped with its drug delivery platform called Siosomes (based on Silane molecules), the company is focusing on the commercialization of its nanotechnology for the improvement and development of pharmaceuticals. The technology provides added benefits to drugs such as enhanced efficacy, decreased toxicity, alternative routes and lower doses of administration. This ultimately translates to lower treatment costs and better treatment management for patients.

The platform can also be used to modulate the immune system in immunotherapy applications. It can provide Intellectual Property (IP) protection to unpatentable compounds such as natural ingredients and biosimilars.

S*BIO

S*BIO was chosen by its peers for its accomplishments in the life sciences industry, and for the significant contributions the company has made to advancing scientific enterprise in the Asia Pacific region. Dr Jan-Anders Karlsson, CEO, accepted the award on behalf of the company. **PA**

Jubilant and Orion Collaborate on Drug Discovery

Jubilant Organosys, headquartered in Noida, India has announced that its subsidiaries Jubilant Biosys (Bangalore) and Jubilant Chemsys Ltd (Noida) have entered into three way drug discovery partnership with Orion of Finland.

Under this "Hybrid & Integrated" arrangement, the Finnish company will have the option of utilizing resources from both of the former's subsidiaries, based on the requirements of Orion's drug discovery projects. **PA**

Draximage and Guerbet to Distribute Nuclear Medicine in Europe

Jubilant Organosys, headquartered in India, has announced that its subsidiary Draximage has signed an agreement with Guerbet for the distribution of nuclear medicine products in Europe.

The partnership agreement will allow the subsidiary to supply nuclear medicine products in European markets including Germany, France, UK, Italy and Spain.

Guerbet will become the exclusive distributor for the sale of Draximage's range of products including, Sestamibi, I-131, MDP DTPA and MAA, through the former's network of European subsidiaries.

"This constitutes a first step for our company in the field of nuclear medicine. It offers benefits for monitoring cardiovascular and metabolic illnesses," commented Philippe Decazes, chairman of the executive committee of Guerbet. **PA**

ReSearch Pharmaceutical Services Acquires Paramax

ReSearch Pharmaceutical Services (RPS), a provider of integrated clinical development outsourcing solutions to the bio-pharmaceutical industry, has entered into an agreement to acquire a privately-held clinical research organization, Paramax International. This is for the consideration of US$1.0 million in cash and 530,973 shares of RPS common stock. The acquisition is anticipated to close in late May 2009, upon satisfaction of certain closing conditions.

When completed, the acquisition will provide RPS with expanded capabilities in the Asian market and complement its current operations in the Americas and Europe. Paramax has its headquarters in Beijing, China with an operations office in Shanghai, and will serve as the former's Asian base of operations.

The shares will be held in escrow and released in three equal portions on the three-month, 12-month and 18-month anniversaries of completion of the acquisition. **PA**

Intas Biopharma to Market Pemetrexed in India

Intas Biopharmaceuticals is launching Pemetrexed under the brand name Pemmet, in India. The drug is used to treat non-small cell lung cancer (NSCLC), a common type of lung cancer caused primarily from smoking and Mesothelioma, a cancer caused by Asbestos exposure.

Simon Daniel, chief executive, marketing, said, "The introduction of Pemmet is going to strengthen our domestic market share in the oncology segment. With the increased prevalence of smoking, lung cancer incidence has also increased in India. It has surpassed the earlier form of cancer – that of the oropharynx, and is now the most common malignancy in males. Occupational exposure is also another cause of lung cancer.

Studies estimate more than 90,000 men and 79,000 women are diagnosed each year with cancer of the lungs and bronchi (the air tubes leading to the lungs). Along with men, the incidence of lung cancer continues to increase in women. The number of lung cancer deaths among women surpasses those from breast cancer. Female smokers may be more likely to develop lung cancer than male smokers.

Dr Chirag Teli, medical advisor, said, "Treatment of lung cancer has opened up new vistas of research and that offer potential of cancer therapy with minimal side effects. The majority of patients with NSCLC eventually develop metastatic disease or disease that is not a candidate for surgical interventions. The drug is used in the treatment of some form of lung cancer in new as well as refractory or relapsed cases, in which previous chemotherapy drug(s) have failed. **PA**

Daiichi Sankyo to Market CS-8958 in Japan

Biota Holdings has announced that Daiichi Sankyo, the co-owner of the neuraminidase inhibitor (LANI) CS-8958, has signed a contract to manufacture and market the product in Japan. This is pending the successful completion of Phase III clinical studies and on obtaining registration approval. Biota, as one of the owners, will receive an undisclosed royalty on sales and a number of fixed sum payments on the achievement of certain sales milestones in the Japanese market.

All other key markets for CS-8958 in the world, including the US, remain available for licensing by the partners. Both companies will share commercial returns from licensing outside Japan.

Patient enrolment of Phase III studies in Asia has been completed with results expected to be released mid year. **PA**

GVK Biosciences Forms Alliance with Excel for Clinical Trials

GVK Biosciences (GVK BIO) and Excel PharmaStudies (Excel) have announced a strategic alliance to conduct clinical trials in Asia. The alliance provides clinical trial sponsors with access to the scientific skills, talent pool, flexible resource supply, and cost-effectiveness of India and China.

India has sponsor-friendly regulations and strength in Phase II/III clinical trials; China's strengths lie in its large market, Phase III and post marketing Phase IV studies. Through the alliance, sponsors will be able to conduct Phase II-IV trials using resources in India and China as required. Under the terms of the arrangement, the companies will help sponsors to conduct and manage Phase II-IV clinical trials, statistical analysis and medical writing. Any trial conducted in India for Excel will be carried out by the GVK BIO clinical research team and will be managed by a core project management team from Excel. Similarly, a GVK BIO China trial will be carried out by the Excel team and managed by GVK BIO's project management team.

"This is a first-of-a-kind alliance between an Indian Contract Research Organization (CRO) and a Chinese CRO. The alliance integrates trial management across both countries and provides sponsors with a single point of contact", said Manni Kantipudi, president, GVK BIO. **PA**

Werum Strengthens Presence in Asia Pacific

Werum Software & Systems, a provider of Manufacturing Execution Systems (MES) for the pharmaceutical and biotech industries, is strengthening its presence in the Asia Pacific region. It has founded a subsidiary in Japan and another in Singapore.

The subsidiaries will reinforce the local support capacities that the company already provides in cooperation with its solution partners in Japan, Singapore, Thailand, China, and Australia.

"Many of our multinational customers with operations in Asia Pacific as well as local manufacturers will improve their manufacturing quality and drug safety in order to meet international standards", says Hartmut Krome, chairman of the executive board. "Our MES product PAS-X will be the key for such improvements. We expect future growth in the region to contribute a rapidly increasing share, with Japan and Singapore as the focal points of the business." **PA**

BioDuro and Roche Expand Collaboration on Drug Discovery

Chinese Contract Research Organization (CRO) BioDuro has announced a strategic partnership with Roche to support discovery phase research efforts at the latter's global research sites. The former will provide research services in the areas of discovery chemistry and biology, which can help to shorten (internal) drug discovery timelines. This agreement is an expansion of an existing relationship.

"Presently, there is intense competition within the CRO industry for outsourcing and drug discovery services, and the expectation is that they will deliver problem solving skills and innovation in both chemistry and biology," commented Robert Goodnow, global head, Medicinal Chemistry Outsourcing, Roche. **PA**

PerkinElmer Opens Training and Logistics Center in India

PerkinElmer has announced the opening of its service training academy and logistics center in Mumbai, India. Dusty Tenney, president, Laboratory Services, inaugurated the center. The facility will shorten the response time to customers as well as improve instrument uptime.

Responding on the timing of the investment and the current economic situation, Dr Fedja Bobanovic, president, PerkinElmer India said, "The service training academy and logistics center demonstrates our continuous commitment to India in supporting the expansion of health and environmental infrastructures of emerging growth nations and our continued focus on customer support. India is a strategically important market for our company, with significant growth opportunities including environmental monitoring, neonatal and maternal screening, and pharmaceutical research." **PA**

Matrix Receives First Tentative FDA Approval for HIV Drug

Mylan has announced that Matrix Laboratories, its India-based subsidiary has received the first tentative approval from the US Food and Drug Administration (FDA) under the President's Emergency Plan for Acquired Immunodeficiency Syndrome (AIDS) Relief (PEPFAR). The approval is for the company's Abbreviated New Drug Application (ANDA) for Emtricitabine and Tenofovir Disoproxil Fumarate Tablets, 200 mg/300 mg.

The tablets are the generic version of Gilead Sciences' Truvada Tablets. Truvada is a second-line anti-Human Immunodeficiency Virus (HIV) drug in the nucleoside reverse transcriptase inhibitor (NRTI or "nuke") family and is used in combination with other medications to control HIV infection. Patients often use second-line therapies if and when they develop resistance to initially prescribed treatments or experience clinical failures. **PA**

Cell-Based Assays: Advancing Discovery

Richard Eglen,
President, Bio-discovery,
PerkinElmer

Primary and stem cells in high throughput screening (HTS) and high content screening (HCS) play an increasingly important role in drug discovery.

The majority of screening assays in either drug discovery target validation or lead compound identification/optimization now utilize cell-based technologies. Many of these assays use miniaturized fluid addition protocols, accompanied by highly sensitive detection techniques and automated liquid handling instruments. One implicit assumption is that in order to achieve an optimal understanding of the physiology of the biological target, as well as its pharmacological interaction with novel compounds, understanding the response in a correct physiological (ie, cellular) context is critical.

Although immortalized cell lines are widely used in cell-based screening, they are not without drawbacks. Historically, classical cell-based assays have used phenotypes more for their ease-of-use and compatibility with screening instrumentation, rather than for their optimal physiological relevance. However, since cell-based assays frequently utilize cell phenotypes that are different from those in native human physiology, one may question the clinical relevance of the validated target, the lead compound identified, or both. Consequently, a growing number of discovery programs are using primary or stem cells in High-Throughput Screening (HTS) and High-Content Screening (HCS) protocols. This suggests that the use of primary cells, HTS and HCS are rapidly converging as enabling techniques in drug discovery.

Cell-Based Assays Drug Discovery

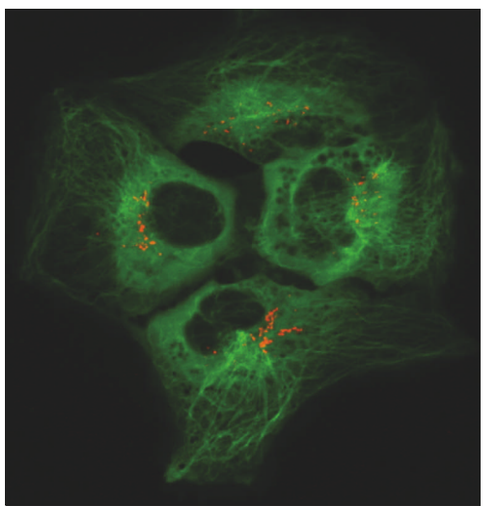
Common approaches in primary screening use assays in which recombinant immortalized cells express a discrete molecular target. The activity of compounds at this target is then assayed using functional responses that are detected and quantified via sophisticated automated liquid handling and detection systems. Recombinant immortalized cells are used to screen large libraries of small molecules. Potential "hits" identified are then "validated" through multiple counter-screens to identify compound potency and specificity.

Via sub-structural searching techniques, libraries can be used to optimize lead compounds for "druggable" properties including solubility and pharmacokinetic characteristics, and potential cellular toxicities. Through the iterative re-screening of focused libraries, the quantification of interactions at molecular targets can result in potential candidates for later *in vivo* and clinical testing. The approach has met with some success in identifying lead compounds for further development. This is despite the occurrences of disparities between compound effects on drug targets recombinantly expressed and *in vivo* efficacy.

Compromises in Using Immortalized Cells

As noted, there are advantages to using immortalized cell lines in drug discovery. First, near-unlimited amounts of transfected cells can be cultured in reproducible batches, providing a consistent, homogenous vehicle for HTS campaigns. Second, they provide a null background for target expression and assay response measurement. The stable expression of drug targets can be achieved for physiological relevance. Additional reporter proteins can be transfected into these cells by using established cloning and expression techniques, for monitoring compound/receptor interactions via gene expression readouts.

However, emerging data indicates limitations in screening compounds using these systems, particularly in regard to the physiological relevance of data generated with respect to human physiology. Indeed the genetic and therefore molecular phenotype of cultured immortalized cells can significantly differ from that of native cells *in vivo*. This raises the question of which functional response one should measure in a HTS assay ie, which response is most relevant in identifying clinically relevant leads.



Retinal epithelial cells labeled for microtubules (green) and mitochondria (red).
(Source: PerkinElmer and Joachim Hehl)

Primary, Stem Cells in HTS

There are differences between the physiological environment when using recombinant cell lines and those found in natural tissue. This understanding has led to an increased interest in using primary mammalian cells for HTS – in which the endogenous target is assumed to be expressed in a setting far closer to that found in the human disease, and at levels that resemble those found endogenously. The presumption is that new potential drugs characterized using primary cells will act more predictably, and in line with disease state interaction, than those characterized by immortalized cells, according to Eglen, Comb Chem & HTS, 2008.

One barrier to the widespread adoption of primary mammalian cells in HTS is their lack of abundance and homogeneity. This is partially offset by the use of highly sensitive assay techniques and miniaturized detection systems, enabling the use of far fewer cells per assay data point. However, the growing availability of embryonic stem cells (ESCs) may provide cells that can be grown in abundance (in a similar

Cover Story

manner to immortalized cells), yet which retain key phenotypic characteristics of natural cells.

Furthermore, ESCs can be differentiated into distinct cell types, corresponding to required organs and tissue, according to McNeish, Curr Op Pharmacol 2007. Surprisingly, few primary cells or ESCs are currently used in primary screening, instead being relegated to secondary screening campaigns or lead optimization studies.

Possibilities for ESCs in HTS

The lack of cell availability restricts the use of primary cells in HTS. However, this may be overcome with the use of pluripotent ESCs, which can be grown in an almost unlimited fashion. These cells can be differentiated into specific cell types including neurons, hepatocytes or myocytes, and protein reporters can be recombinantly engineered and inserted. Transfected ESCs can be selected, expanded, and then using specific growth factors, induced to differentiate into populations enriched for a selective lineage (eg, neurons, myocytes, and hepatocytes).

According to Pouton, CW and Haynes, JW Nature, 2007, although human ESCs provide considerable advantages in screening, their disadvantages are that they do not propagate and divide, while being difficult to maintain and expand. An alternative is to use human induced pluripotent stem cells, which can be obtained from cord blood, bone marrow and several other tissue.

The advantages of ESCs include the use of previously unavailable cell types and the ability to study cellular regeneration and differentiation. Small molecules have historically been recognized to reproducibly impact the differentiation of stem or progenitor cells. The increased expertise in human stem cell cultures to facilitate HTS has allowed the identification of new chemical series that serve to direct cellular renewal, regeneration, expansion and differentiation, particularly when used with adult pluripotent stem cells (iPS cells).

High Throughput Imaging

Primary human cells are used in several therapeutic areas, and such biologically relevant cell assays are becoming increasingly recognized as robust and amenable screening tools for HTS. Cellular imaging is emerging as an important tool that integrates biological complexity into drug discovery. Current imaging systems allow the high-resolution analysis of single cells, high throughput and kinetic studies on live cells, and are linked to efficient data storage systems via user-friendly image analysis programs.

The key feature of modern cellular imaging systems in drug discovery is to provide a multidimensional aspect for each experiment performed, allowing the measurement of multiple parameters, which in turn enables the analysis of cellular responses against different stimuli, according to Yarrow, Comb Chem & HTS, 2008. ESCs permit the development of predictive screening assays that can deliver higher-quality leads. The emergence of high content imaging instruments coupled with plate handling equipment also allows high throughput assays to be carried out successfully by imaging target cells within heterogeneous cultures.

One area that is benefiting from screening via automated confocal imaging systems is the ability to undertake a cellular phenotypic approach to drug discovery. The use of HCS techniques to permit phenotypic profiling of compounds based on changes in cellular activity looks likely to grow in drug discovery. However, this will require the development of techniques to analyze large image datasets, as well as precise correlations of phenotypic changes and compound mechanism of action, according to Young, Nature Chem Biol, 2008. **PA**

Enquiry code: 093E01

Looking Ahead

The use of cell-based assays in all phases of drug discovery, and notably in HTS, has accelerated in the last five years. In many screening campaigns, the cell phenotype has been subservient to assay technology, instrument, or liquid handling systems in the laboratory. Consequently, heterologous expressions in immortalized cell lines of G protein-coupled receptors (GPCR), ion channels or kinase targets, as well as their ancillary signaling partners, provide the mainstay of most cell-based screening assays. Clearly, such cells are poor substitutes for cells reflecting human diseases.

Furthermore, current cell-based Absorption, Distribution, Metabolism, and Excretion/Toxicity (ADME/Tox) assays, now moving into HTS, are relatively poor predictors of the human response due to the nature of the cells being used in the studies. Because of these limitations in standard HTS programs, the growing interest in the use of primary cells and ultimately stem cells in drug discovery is increasingly justified.

The use of primary cells in secondary screening assays is also increasing apace, particularly in studies where confocal imaging is used, as well as in target validation studies in conjunction with gene silencing techniques. The convergence of high throughput confocal imaging, primary cells and stem cells are likely to collectively allow the earlier and more effective identification of novel clinical candidates.

Inspection Technology Eliminates Cross Contamination

Angela Dove,
Writer

The combination of Near-Infrared (NIR) visioning and high-speed tablet sorting technologies ensures physical and chemical integrity in tablets.

Conventional tablet inspection methods, whether manually with the naked eye or accomplished through high-speed automated sorting machines, are only able to recognize when a product is physically complete. Variations in attributes like wrong color, misaligned or missing printing, chips, breakages, holes and other physical defects in the tablets can all be easily spotted. However, conventional vision is unable to detect any deviations in the chemical components of the tablet.

Molecular Level Detection

Owing to its ability to inspect objects at the molecular level, Near-Infrared (NIR) technology is widely used in industries such as packaging, as an accurate and efficient tool to ensure quality. In pharmaceuticals, it can be used to identify the chemical properties of components used in tablets. A comparison of chemical signatures against a pre-established sample will then reveal if the correct dosage of Active Pharmaceutical Ingredients (API) have been used in the product.

The combination of VisioNIR from Uhlmann VisioTec and Proditec's tablet sorting machines enables the accurate inspection of individual products. This pertains to physical and chemical properties such as composition and concentration levels of active ingredients.

Traditionally, only time-consuming chemical sample testing in the laboratory has been able to determine compliance in the levels of APIs used in tablets. With NIR technology however, manufacturers have the capability of checking for chemical compliance in tablets during high-speed machine sorting as well.

The technology is able to detect the presence of ingredients down to a concentration level of one percent. Subtle changes in density that indicate problems with the production process can also be detected. Tablets are checked at a rate of up to 200 per second, making the technology suited to the requirements of modern day mass manufacture.

Parameters of Pharmaceutical Tablets Checked	Visual Inspection Systems	VisioNIR Technology
Presence	✔	✔
Shape	✔	✔
Colour	✔	✔
Cracks	✔	✔
Splinters	✔	✔
Dimensions	✔	✔
Stains, spots, hairs, etc.	✔	✔
Logo or text (printing)	✔	✔
Logo or text (engraving)	✔	✔
Wrong Composition	✘	✔
Different Concentration	✘	✔
Wrong Product – Same Shape and Colour	✘	✔
Wrong Product – Similar Geometry	✘	✔
Active vs Placebo	✘	✔
Quality Inconsistencies	✘	✔

Differences between normal vision inspection systems and VisioNIR technology. (Source: Proditec)

In line with conventional practice, any batch of pharmaceuticals failing quality assurance inspections is left with only two options – to be entirely destroyed or to be placed through a second round of labor-intensive manual sorting. Neither of these two choices – the first, financially prohibitive and the second, time-consuming – are ideal solutions.

Inspection Process

By implementing NIR-installed batch sorting machines in the production line, these problems can be overcome. One advantage is the ability to accomplish checks for the physical and chemical quality of the product on the production line, prior to packaging. Any defective tablets are ejected before reaching the packaging stage, eliminating the need to re-package and allowing cost savings to be realized.

A tablet is first made to pass through a beam of light. By using NIR-spectroscopy, the system gathers the reflected light and compares the signature in the NIR-spectrum against a sample model. Any variations in the physical and chemical parameters of the product are reflected by changes in its spectrum. These changes are detected and recognized by the system as a qualitative defect of the inspected product. Tablets determined to be out-of-specification can then be safely ejected, thereby preserving the medical integrity of the batch.

This combination of technologies creates a tool with which to check tablets for correct levels of API, cross contamination or to determine if the product is active or a placebo.

The challenge of ensuring product safety in the modern mass manufacture environment is in ensuring that the physical attributes and chemical signature of a product fall within specifications. High-speed tablet sorting combined with NIR technology enables a complete product inspection while maintaining productivity and efficiency. **PA**

Enquiry code: 093E02

Drug Packaging: Closed IV Systems to Lower Costs and Infection Risk

Koh Sok Tiang,
Director, Technical Services & Business Development, Asia Pacific, West Pharmaceutical Services

To address the risk of nosocomial infections in hospitals, the closed intravenous (IV) system offers a safe and effective means of packaging and delivering drug fluids.

The safety of IV therapy requires that the system is free from particulate contamination and micro-organisms including pyrogens. The presence of any of these can affect the health of patients receiving treatment. This means that the fluids and the accessories for IV therapy, such as the devices used to access the vascular system, catheters, infusion devices and tubings must be sterile and free of micro-organisms.

Despite taking these precautions, there are instances where patients can still acquire infections in the hospital through exposure to pathogens. Such exposure may be due to the invasive nature of procedures carried out on patients which increase the risk of infection. It may also be attributed to their already compromised state (due to their health condition) and their passive exposure to normally occurring bacteria in the hospital environment.

Infections acquired in the hospital setting are commonly known as nosocomial infections and it is the hospitals' duty of care to reduce such infections wherever possible.

Benchmark for Quality of Medical Care

A key benchmark, Average Length of Stay (ALOS) is often used as one economic measure to gauge the quality of medical care in terms of optimizing a patient's stay between good health and economic outcomes. If the level of nosocomial infection is high, it means that patients will be likely to extend their stay due to acquired infections in the hospital. This can affect the reputation of the hospital.

This also means that the hospital will have fewer patients over the same period. As a large percentage of the revenue is generated during the first few days of admission, this is likely to lower the profitability of the hospital.

ALOS is defined as:

Total number of days stayed per specific group

Total number of discharged patients for the same group

Or:

Total number of days of care (includes date of admission, not discharge)

Number of patients

In India, studies have shown that the ALOS in Intensive Care Units (ICU) without any hospital acquired infection is 4.4 days. But when hospital acquired infection increased, the need for the patients to prolong their hospital stay to manage those infections also increased to 9.4 days. In a separate study, the ALOS in China was shown to be as high as 16-17 days. Such figures illustrate the importance of reducing the possibility of nosocomial infection. Hospitals in western countries vary in their ALOS but average around 6.1 days – which includes both ICU and general wards.

Open vs Closed IV Systems

Studies have been conducted to identify the sources of contamination and the possible means to reduce them. One of the most common sources of nosocomial infection identified is via the use of an open IV System.

There are generally three types of IV fluid containers in use globally. These are:

a) Rigid containers which are made of glass, High Density Polyethylene (HDPE) or Polypropylene (PP)

b) Semi-rigid containers which are made of Polyethylene (PE) or Polypropylene (PP)

c) Flexible bags which are made of polyvinyl chloride (PVC), or Polyolefin laminate

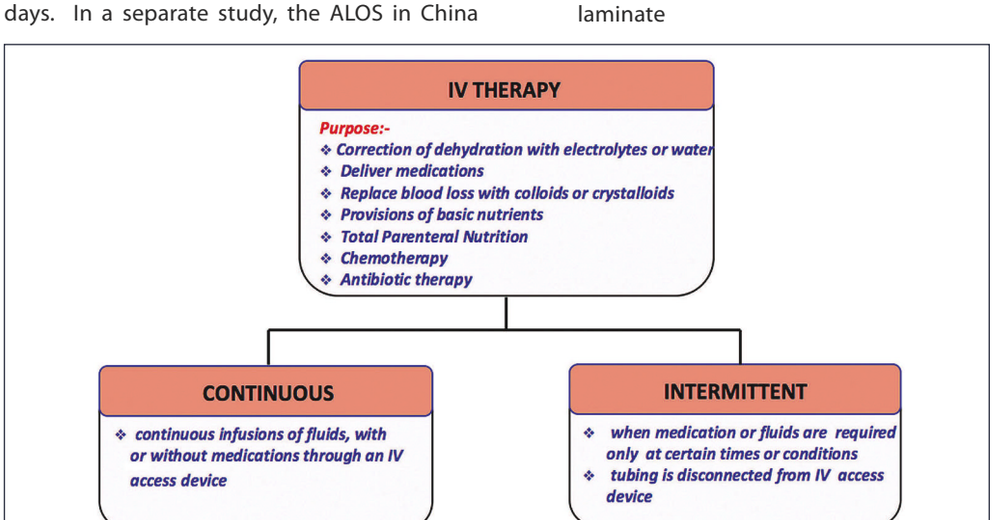


Figure 1: Application of IV Therapy. (Source: West Pharmaceutical Services)

The open IV system typically consists of a glass bottle or rigid plastic container. For the fluid in the container to egress into the vein of the patient, it must be externally vented to ambient air due to the non-collapsible nature of the rigid container. The risk of airborne contamination is therefore significantly greater, especially if the air is not filtered.

In addition, the external venting with air bubbling would further increase the risk of infection. In some countries where the rubber closure used is made of natural rubber elastomer, viable fungi may be present even after autoclaving. This presents another source of infection.

A closed IV system is a feasible alternative as it does not require any external venting with ambient air to effect the flow of fluid from container to patient. Collapsible bags and specially configured semi-rigid bottles are able to achieve this.

Acceptance of the Closed IV System

In certain countries, a closed IV system is the minimum acceptable standard – based on the countries' regulatory agencies and hospitals. It is dependent on the understanding of the inherent risks associated with open IV systems and the knowledge that such risks can be easily avoided by a switch to a closed IV system. The main reasons are:

a) Patient benefits in terms of safety and reduced infection risk.
b) Improved patient health outcomes.
c) Reduction in the costs incurred by patients and hospitals – a result of patients not prolonging their stay in hospitals.
d) Improved quality care delivery in hospitals.
e) Meeting the key goals of regulatory authorities to ensure that best practices are adopted where possible, to continually improve patient safety and duty of care within the hospital setting.

Intravenous (IV) therapy, a technique established more than fifty years ago, is defined as the transfer of a liquid substance directly into a vein. It can be used in acute care and invasive procedures where the requirements for drug or blood delivery is likely and in at least 90 percent of all hospitalized surgical patients. IV therapy is used to correct electrolytes or water imbalances and also to provide nutrition for patients receiving total parenteral nutrition. Today, its application has increased in scope (figure 1).

The administration process can be continuous or intermittent. Since liquid substances in IV therapy are administered directly into the veins, the effect on the human physiology is immediate. Due to this reason, the safety aspect of the therapy is important, particularly when the patients may be under intensive care treatment.

Closed IV systems eliminate one of the most likely sources of nosocomial infection. These systems are beneficial to patients from a safety and efficacy perspective and can achieve substantial cost savings by avoiding unnecessary extended stays in hospitals and drug treatment. This type of drug packaging and delivery is synonymous with best practice and is making inroads into developing countries after being adopted as the minimum standard in North America, Europe and Australia. **PA**

Enquiry code: 093E03

China: Assessing the Need for Outsourcing

Jim Zhang,
President and MD,
JZMed

China offers significant cost advantages to companies that are looking to outsource their R&D activities

The pharmaceutical and biotechnology industries have not been immune to the current financial crisis. It appears that the sector which is the hardest hit is the biotechnology R&D sector – in particular smaller drug companies that are in early stage drug discovery and/or development.

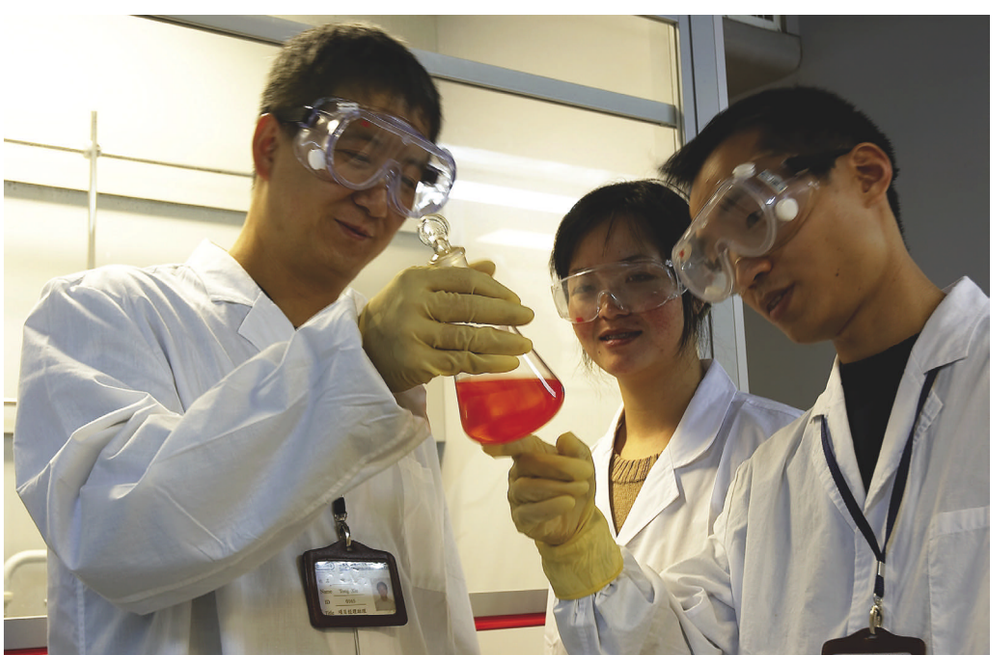
Since November 2008, more than 45 biotech companies have announced reductions in their workforce. The percentage of job cuts within these companies range from five percent to as high as 93 percent. Many have also announced the reprioritization of their R&D programs with more focusing only on late stage development. Several have completely terminated early stage programs including those still in discovery and preclinical research. Others are planning to close their R&D facilities or put their programs on hold.

However, it appears that most of the major pharmaceutical and biotech companies have not been affected by the crisis, probably because of their strong cash reserves. To some extent, many of them could benefit from it as they are poised to acquire more drug candidates which are in the advanced development stages, from the smaller biotech companies that are in financial trouble.

Financial Considerations

The present financial crisis has created a dilemma for R&D oriented drug companies. On the one hand, the nature of drug research and development requires these companies to have abundant cash reserves, which in the past was generally realized through rounds of fund raising.

On the other hand, the crisis has directly resulted in a funding shortage as many Venture Capitalists (VC) or investment institutions have either lost a large chunk of their investment elsewhere or have become stuck with their current investments. This has put them in a less advantageous position to take up other investments. VCs that still have cash in hand tend to be wary as it is unlikely for biotech companies to go public in the near future, given the overall financial situation. The overall climate has been reflected in the reportedly lowest number of biotech Initial Public Offerings (IPO) in 2008, in a year-by-year comparison for the period 2004 – 2008.



Outsourcing to China can help a company achieve a cost saving of at least 60 to 70 percent. (Source: JZMed)

Small biotech companies that do not have strong financial resources, have to think about how they can survive the financial crisis as many VCs are cutting back on investment activities. Many in the industry believe that there are two options for these cash-strapped biotech companies to consider at this moment:

1) Selling their drug candidates or even the entire company at a significant discount.

2) Outsourcing R&D projects to low cost areas such as China, so that they can still continue their programs even with a limited cash reserve.

The first option works for companies that have developed a series of lead compounds. Some of them would have entered the development stages for drugs that are already demonstrated promising results. The situation is more challenging for those that are still in the discovery stage or early preclinical development stage, as some VCs who have invested in startups or early stage biotech companies are currently selling their stakes at a discount of 10-60 percent of the original investment price. For such companies, the second option could be the better choice.

Outsourcing Overseas

The offshore outsourcing of drug R&D programs to developing countries including China, has not been popular with many biotech companies. However, the abrupt change in the financial and investment environment may be a

compelling factor for a shift in mindset. These regions offer significant cost savings, allowing such companies to continue their R&D programs even with limited cash reserves.

At present for example, outsourcing to China can help a company achieve a cost saving of at least 60 to 70 percent. For contract research projects in the lead discovery/optimization area, the current average Full-Time-Equivalent (FTE) rate in most Chinese Clinical Research Organizations (CRO) for a scientist located in Shanghai or Beijing is about US$85,000-US$100,000 per annum. In comparison, a scientist in a similar capacity in the US would cost about US$260,000.

China also has abundant animal species such as rodents, rats, dogs, monkeys and other non-human primates – available at low cost. For example, a monkey in China only costs about US$700-800. For preclinical testing, a two-month animal trial in primates costs about US$25,000-US$30,000.

Companies may also be able to achieve higher levels of productivity by outsourcing to China. They can take advantage of the 13-hour time difference and run their projects 24 hours a day. For example, their internal staff can design and revise the instructions of the project and then forward these to the Chinese service provider, whose scientists can conduct experimental investigations while the US site has closed for the night.

Due to rapid development for over nearly a decade, there are currently a large number of service providers in China to choose from. This outsourcing environment provides flexibility to companies who require these services. For example, companies can begin the business relationship with a short-term contract with a selected service provider. The initial size of the project can also be kept small. The scope of the projects can then be extended and expanded at a later time, if the outsourcing company feels comfortable with their Chinese partners.

Service Capabilities of China's Outsourcing Industry

At present, the Chinese outsourcing industry is composed of about 250 professional service providers with various service capacities and capabilities. Although none of them are likely to be able to provide a fully integrated service yet, the industry as a whole can offer various types of services covering the entire value chain from drug discovery and development to manufacturing.

Besides this, there are about 50 multinational service providers that have service facilities in China. The entrance of these Multinational Organizations (MNO) has raised the service quality and capability of this industry segment. In addition, growing numbers of traditional Chinese pharmaceutical and R&D-oriented biotech companies are also joining the service community as "part-time" service providers, as they are being approached by a growing number of overseas drug companies.

• Early Stage Drug Discovery

China is one of the hot spots for pharma/biotech companies that are looking for compound libraries which possess the structural features of drug-like molecules. The country has a huge pool of skilled synthetic organic chemists and biochemists.

Companies specializing in the synthesis of specialty chemicals, scaffolds and building blocks as well as isolation and purification of natural products from the Traditional Chinese Medicines (TCMs) are spread out throughout the country. Rare chemicals that cannot be sourced elsewhere may be available in China. And because of low labor costs and less stringent environment protection measures, many chemicals and biological agents that cannot be profitably manufactured in other countries may be available in China at reasonable prices.

Drug Discovery

This service has been explored in the past by many major pharma/biotech companies. There are currently more than 30 such service providers that possess focused compound libraries of various sizes.

Besides these focused compound libraries, Chinese service providers also cover all areas of early stage drug discovery. For example, there are more than 20 companies that provide services related to target identification and validation such as DNA sequencing, elucidation of protein structures, reconstruction of proteins, preparation of recombinant proteins and disease modeling.

In addition, there are more than 40 CROs providing services in medicinal chemistry-related research such as lead discovery and optimization; assay and assay method development; and pharmacological property studies such as the determination and optimization of Pharmacokinetics and Pharmacodynamics (PK/PD). Many of them also possess advanced techniques and experience in areas such as high-throughput screening, computer-aided drug discovery (CADD) and structure-activity-relationship (SAR) studies.

Most of the clinical trials conducted in China have been performed by major pharma companies or multinational CROs. (Source JZMed)

• Preclinical Research

There is a group of about 37 China-based companies that provide services in preclinical research including in vivo efficacy testing, in vivo/in vitro Absorption, Distribution, Metabolism, and Excretion (ADME) screening, plasma protein binding studies, metabolite profiling and an entire scope of toxicity studies.

However, the quality of service in this sector was not available until recently. The rapid change of landscape in this area is largely attributed to the entrance of experienced multinational CROs – all lured by the abundant animal species in a favorable regulatory environment as well as readily available manpower resources at low cost. For example, several CROs currently offering services in China are actually the service divisions, branches or subsidiaries of CROs based overseas.

Examples include Bridge Laboratories and Crown Biosciences. The headquarters of these CROs are based in Western countries (mostly in the US), but the bulk or all of their services are performed in China.

In addition, several multinational CROs have formed joint ventures or partnerships and some have ended up acquiring their Chinese partner. For example, Charles River Laboratories has formed a joint venture with BioExplorer while MPI Research has formed a similar relationship with Medicilon.

• Clinical Research

Contract clinical research has been conducted in China for more than a decade. In addition to a vast pool of treatment-naive patients, the nation also has specialized hospitals that posses medical facilities, specialists and knowledge in specialty areas such as cancer.

Drug companies have also realized that China has a pool of well-trained hospital physicians, thanks to the training provided by many Western companies including multinational CROs and major pharma companies. The majority of these medical personnel and other medical resources are located in major Chinese cities. For example, Astra-Zeneca has established a training center at Number Three Hospital of Beijing University to train physicians for clinical trials.

So far, most of the clinical trials conducted in China have been performed by major pharma companies or multinational CROs. Almost all multinational CROs including Quintiles, MDS, PPD and Covance have clinical trial centers there. Pharmaceutical companies including Astra-Zeneca, Pfizer, GSK and Sanofi-Aventis also run clinical research centers. An increasing number of locally-founded contract clinical research organizations have also emerged. At present, there are a total of 47 such CROs in China.

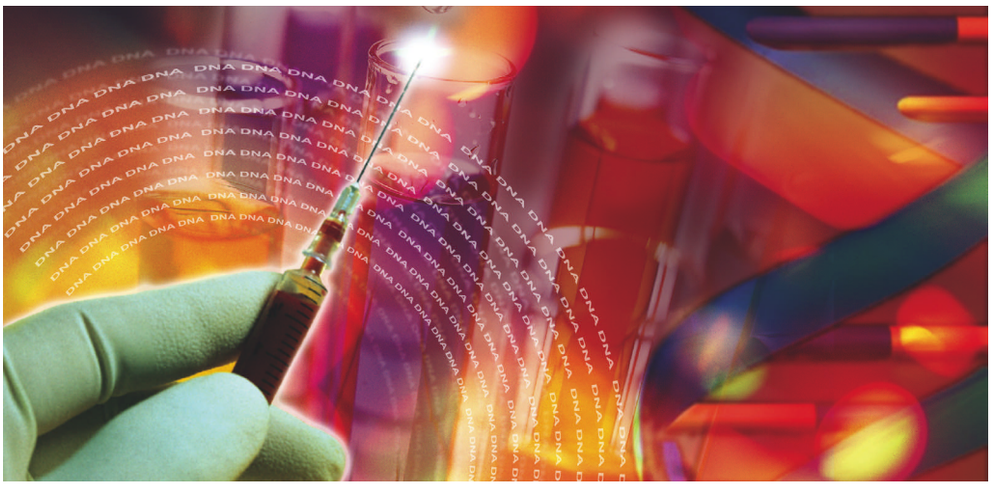
• Process R&D

Among the various service sectors in the Chinese pharmaceuticals outsourcing industry, process R&D and contract manufacturing of Active Pharmaceutical Ingredients (API) for developmental drugs are the most active. There are about 60 professional service providers in this sector. The majority of them also posses strong capabilities in process research and development with decent-sized process R&D teams as well as advanced pilot plants for step-by-step process up-scaling.

Their facilities are also generally supported by an internal Quality Control/Quality Assurance (QC/QA) laboratory equipped with advanced analytical instruments such as High Performance Liquid Chromatography (HPLC) with both regular and chiral columns, GC, LC-MS, etc. The majority of them have production capacities that range from multi-kilograms to low-end metric tons (with reactor volumes ranging from 50L to 3,000L), and are able to handle a variety of chemical transformations. Technologies for certain special chemistry tasks such as large scale chiral resolution are also available.

Geographic Distribution of Service Providers

At present, China-based service providers are densely located in Shanghai and Beijing.



These two cities (including their vicinities) house more than 90 percent of China's professional service providers. Shanghai has more CROs/ Contract Manufacturing Organizations (CMO) in chemistry-related services such as drug discovery research and contract manufacturing, whereas Beijing is more popular with CROs that provide biology-related services such as preclinical and clinical research.

The issue of Intellectual Property (IP) protection has been the major concern to companies that are considering outsourcing to China. While the situation has been improved in recent years, companies may still need to address the following issues:

• Appropriately assess the projects to be outsourced: As rule of thumb, projects to be outsourced should be appropriately classified to determine their IP risk tolerance level. Based on this assessment, outsourcing companies can then decide on the activities that should be outsourced and which service provider to select.

• Identify the right service provider: When selecting a service provider, both the technical skills and service quality/reputation of an interesting vendor must be considered. However, larger CROs/CMOs may not necessarily be better than the smaller ones. It is advisable to obtain references from other companies that have previously engaged in outsourcing activities in China.

• Effectively manage outsourced projects: Once the outsourced project has started, it is critical for outsourcing companies to appropriately manage the outsourced projects, including developing a healthy relationship with the Chinese service provider. **PA**

Enquiry code: 093E04

Talent Acquisition in Emerging Markets: Staff Shortage *(Part One)*

Martin Reynolds
Chief Executive Officer,
Sharpstream Life Sciences

In the emerging pharmaceutical markets of Asia Pacific, supply of labor appears to be struggling to keep up with fast-growing demand.

Hampered by generic competition and an increasingly tough pricing and regulatory environment, the developed pharmaceutical markets of the US and Europe are slowing. The established multinational companies are no longer able to rely on double digit price increases and line extensions, and are unable to replace lost sales with new and innovative products from their research and development pipelines. These companies increasingly see sales generated in emerging markets as an important component of future growth.

Asia looks set to become the largest regional pharmaceutical market in the world. China has posted market growth of over 20 percent per annum for the last decade, and this expansion looks set to continue, with the market forecast to reach a value of US$41 billion in 2012. Smaller countries such as Malaysia and South Korea are also recording rapid market growth. Vietnam is emerging as a nascent manufacturing centre, and Singapore has a growing reputation as a biotechnology hub.

In a survey of pharmaceutical executives published by PricewaterhouseCoopers in 2007, more than half believed that the global centre of gravity of the pharmaceutical industry would be in Asia in the near future.

Perceived Expectations

This shift is borne out in another survey, in which executives at corporate level were asked to rate the strategic priority given to the emerging regions by their companies. With just one exception, all of the executives surveyed say that Asia Pacific has been given either a High or a Very High strategic priority within their company (Figure 1.1).

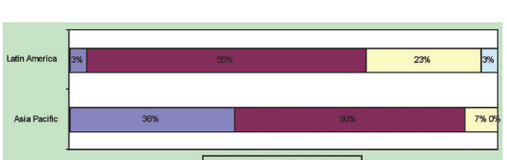


Figure 1.1: Level of priority given to Latin America/ Asia-Pacific in the company's global strategy. (Source: Sharpstream Life Sciences)

It must be emphasized that, in the rush to embrace the putative future of the industry in Asia, the markets of Latin America should not be ignored. Many markets there have grown faster than the developed markets in recent years, and are likely to do so in the future, fuelled by growing, aging populations and strong economic growth. Although the interviewees are slightly less enthusiastic in their assessment of Latin America's place in corporate strategy, most executives still see the territory as having a High strategic priority.

In total, the Latin American regional market was valued at US$42.5 billion in 2007 and has recorded a compound annual growth of 13 percent over the last five years. With sales of US$15.7 billion in 2007, Brazil has become the tenth largest pharmaceutical market in the world, fuelled by double-digit sales growth.

While growth in Mexico has slowed, it is still a significant market of over US$11 billion and has become a regional manufacturing hub for many multinationals. Argentina has also posted double-digit growth figures in recent years, and Venezuela's market, driven by burgeoning oil revenues, has taken off, more than doubling in size in the last three years.

In 2005, McKinsey estimated that the global pharmaceutical industry would employ approximately two million people worldwide in 2008. Although only around a fifth of this workforce is currently employed outside of the three main markets of the US, Europe and Japan, this proportion is growing fast. The industry has been building its presence in both Asia Pacific and Latin America for some time, and most big pharmaceutical companies now carry out a range of activities, including manufacturing, discovery research and clinical development.

In Latin America for instance, the number of clinical trials conducted annually has risen tenfold in recent years. The multinational industry has also built up a significant and rapidly growing commercial presence in the major emerging markets. They have in the process acquired a voracious need for skilled and experienced management talent.

In China, whilst almost all multinational pharmaceutical companies have a presence there, not one has yet captured the country's full potential. McKinsey believes that, to serve China effectively, multinationals will require a much bigger presence in the country, including bigger sales forces. It estimates that to meet their growth aspirations in China, global pharmaceutical companies will need to add at least 11,500 new medical representatives by 2011, an increase of over 18 percent per year. To accomplish this task, the industry will have to find and nurture new sources of talent.

The pharmaceutical industry is both a knowledge industry and a people industry, and this is as true in emerging markets as it is in developed markets. Talented people are one of the most important resources for any pharmaceutical company, and how that company recruits and develops such individuals is the competency that will set it apart from its competitors.

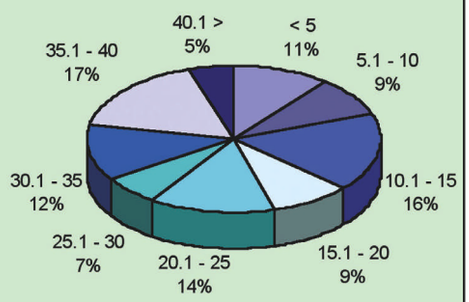
This study looks exclusively at two regions: Asia Pacific, encompassing China, Hong Kong, Malaysia and Singapore; and Latin America, including Argentina, Brazil, Chile, Colombia, Mexico and Venezuela (Figure 2.1).

The survey was broken into two sections, with the first focusing on the in-market perspective in each country, interviewing senior executives in the local office of each multinational (often several from the same company). The second focuses on the Corporate and Regional Headquarters (HQ) view, interviewing executives with responsibility for one or both of the regions studied.

The Emerging Markets' Executives

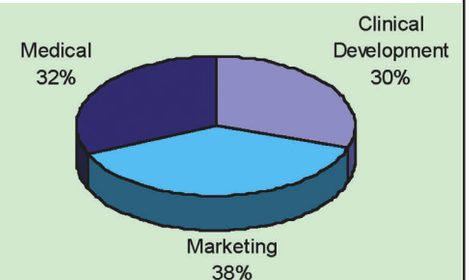
Between August and September 2008, 122 pharmaceutical executives in emerging markets in the Asia Pacific and Latin America regions

Global company revenues, 2007 ($bn)



The in-market interviewees working for a range of multinational companies.

Job function of in-market interviewees

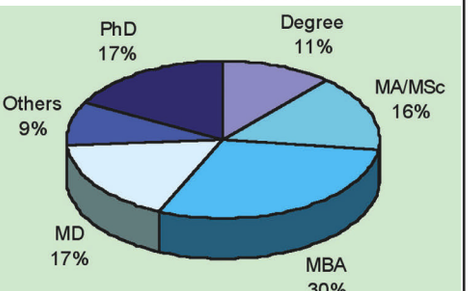


The in-market interviewees are evenly split between Marketing, Medical Affairs and Clinical Development.

Demographic profile of in-market interviewees

The majority of the in-market interviewees are local.

Demographic profile of in-market interviewees



Most of the in-market interviewees are well educated.

Figure 2.1: The In-Market Executives. (Source: Sharpstream Life Sciences)

were interviewed. These individuals hold Director level and higher positions in one of three job functions: Marketing, Medical Affairs and Clinical Development. They have been in their current positions for an average of almost three years, and each directly manages an average of eight people, although some are responsible for 40 or more.

The interviewees work for a range of multinational pharmaceutical companies (all headquartered in either the US, Europe or Japan), with 80 percent employed by companies with global revenues of US$10 billion or more. All of the big pharmaceuticals companies are represented, as are several leading biotechnology companies.

The majority of the interviewees (75 percent) are local executives who have worked in their home country all their lives, with a significant minority (20 percent) being expatriates from outside the region, usually from the US, Europe or Japan. The remainder are either "returnees", ie, local executives who have worked abroad for part of their careers but have returned to their home country (3.0 percent), or "regional expatriates", ie, secondees from another country within the region (2.0 percent).

The Corporate Headquarters Executives

Separately, a group of 30 senior executives, located at the corporate or regional headquarters of a range of multinational pharmaceutical companies based in the US and Europe, were also interviewed. These individuals hold senior executive level positions in the corporate headquarters with specific responsibility for one or both of the regions studied. Just over half are responsible for Latin America exclusively, while the remainder are responsible for either Asia Pacific by itself or in combination with another emerging territory. (Figure 2.2)

The Results

Major Challenges

The interviewees at both in-market and corporate level were questioned on the major challenges facing the industry in each region. The results are illustrated in Figure 3.1, Figure 3.2 and Figure 3.3 and Figure 3.4.

• Shortage of Talent

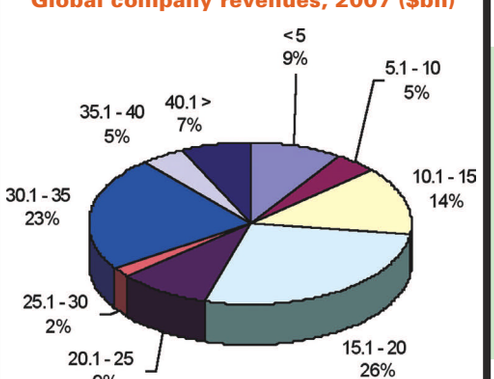
Most of the in-market executives interviewed in Asia Pacific agree that a shortage of talent is the biggest issue facing the pharmaceutical industry in their region. When asked about the top three challenges for the industry, 64 percent of respondents cite problems with a lack of talent in the region.

Partly because of the lack of qualified locals, the leaders of most multinational pharmaceutical companies' subsidiaries in China are foreign citizens. In a survey of 33 multinational pharmaceutical companies in China, 28 said that their general managers were foreigners.

Sources of new talent are limited. Traditional education and labor markets provide few people with the right qualifications and experience. In China, the leading medical schools graduated just 6,200 students in 2005, and specialized pharmaceutical colleges just 3,900. Additionally, although business schools and management training institutions have proliferated in recent years, apart from an elite few, it is difficult for companies to tell which schools produce skilled managers.

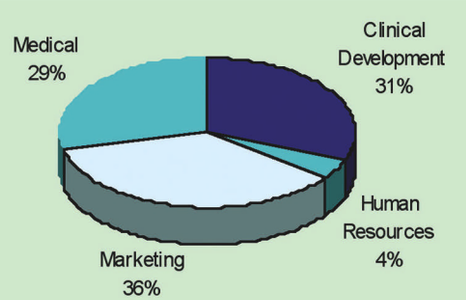
This shortage not only makes it difficult to recruit good people in the first place, but also to retain them. Companies that are suffering from the same talent shortage are only too willing to tempt high-performing individuals away from their current jobs. Because of this, there are

Global company revenues, 2007 ($bn)



The corporate headquarters interviewees work for a range of multinational companies, from the relatively small to the very large.

Job function of corporate headquarters interviewees



The corporate headquarters interviewees are evenly split between Marketing, Medical Affairs and Clinical Development, with an additional small representation from Human Resources

Figure 2.2: The Corporate Headquarters Executives. (Source: Sharpstream Life Sciences)

Drug Manufacturing

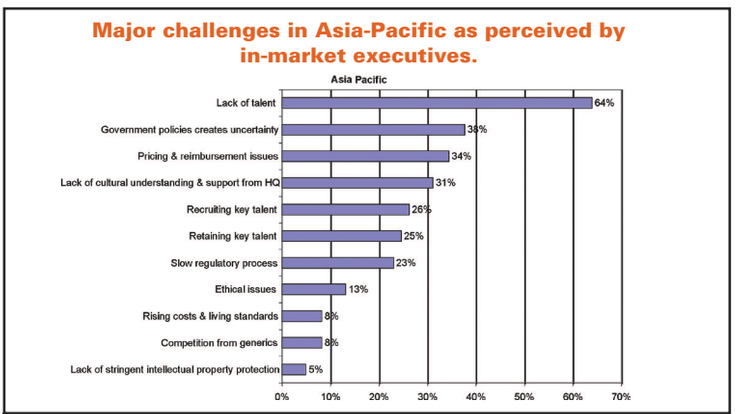


Figure 3.1: The biggest challenge facing the pharmaceutical industry in Asia-Pacific is a lack of talent. (Source: Sharpstream Life Sciences)

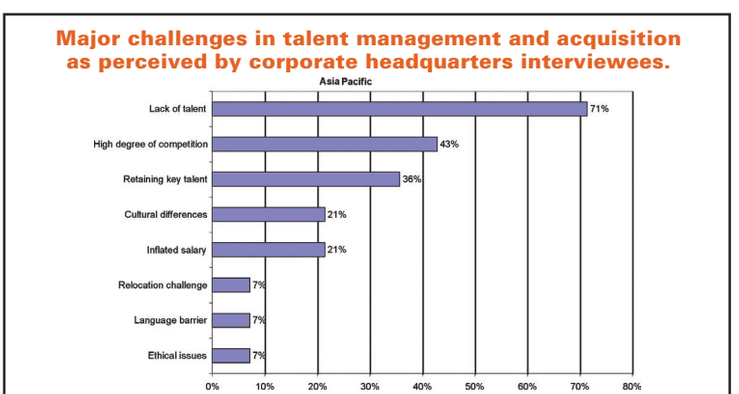


Figure 3.2: The talent shortage in Asia-Pacific is recognized at corporate level. (Source: Sharpstream Life Sciences)

Figure 3.3: Lack of talent is not seen as being such an important issue in Latin America. (Source: Sharpstream Life Sciences)

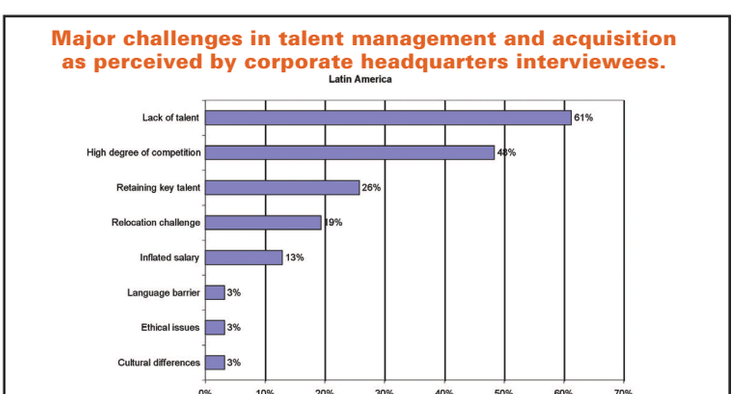


Figure 3.4: The talent shortage in Latin America is recognized at corporate level. (Source: Sharpstream Life Sciences)

signs that the labor market in much of the Asia Pacific region is moving in favor of the employee and away from the employer.

Notably, a lack of talent is not seen by in-market interviewees as being a major problem in Latin America, with just 13 percent citing it in their list of challenges in the region. Nevertheless, when those at corporate headquarters were questioned on the main challenges in talent management in the region, top of their list was the lack of talent.

Corporate leaders in Asia Pacific have a similar assessment of the challenges facing talent management, as their peers in Latin America. In both regions, the corporate interviewees rank Lack of Talent, Competition for Talent and Retaining Key Talent, in that order, as being the top three challenges (Figure 3.2 and Figure 3.4).

• Regulatory Challenges

Some of the other challenges shown in Figure 3.1, Figure 3.2, Figure 3.3, and Figure 3.4 show how important it is to recruit and retain leading management talent locally, rather than parachute it in from corporate headquarters or elsewhere. According to the interviewees, some of the most pressing problems for the industry in both regions pertain to relationships with government, regulators, and payers – including pricing and reimbursement, government policies, and the slow regulatory process.

Especially in China, multinationals continue to face the barriers to market entry, including capital requirements, weaknesses in the intellectual property regime and other regulatory obstacles. According to Peter Mandelson, previously the EU Trade Commissioner, European companies often complain of encountering in China, "an unspoken economic nationalism that implies that foreign investment is no longer wanted or needed".

In Latin America too, the operating environment can be difficult for pharmaceutical companies. Although drug pricing remains relatively free in most of the region, the introduction of direct price controls is a growing threat in many countries. And in Venezuela, where the market is growing at a rate of over 30 percent every year, intellectual property rights are under attack (no pharmaceutical patents have been granted since 2003), restricting the ability of multinationals to share in that growth.

There is little doubt that multinationals in both Latin America and Asia Pacific operate in environments that are more challenging than those in the US and EU, particularly in the regulatory space. The leading pharmaceutical companies in the US and Europe have highly-developed clinical, regulatory and medical affairs departments, staffed by experienced individuals. Many of them have previously worked in the relevant drug approval, pricing and reimbursement agencies and bring with them valuable knowledge and networks of contacts.

To build such relationships with regulatory agencies, payers and key opinion leaders in emerging markets – a company's representatives must be socially and culturally aware, and highly sensitive to local business practices. It will usually, though not always, be easier for a local person to navigate these waters than it will be for an outsider. However, in many emerging markets – China in particular – there is no established talent pool with these niche skills.

Unfortunately, if talented local people are in short supply, a company will have to either employ less able locals, or foreigners. The quality of the team negotiating with these organizations will suffer, with predictable results. Therefore, difficulties faced by multinationals in the regulatory, pricing, and even commercial environments can be directly linked to the talent shortage. **PA**

Part two of the series will be featured in the Jun-Jul issue of PharmaAsia

Enquiry code: 093E05

Outsourcing: Meeting Standards

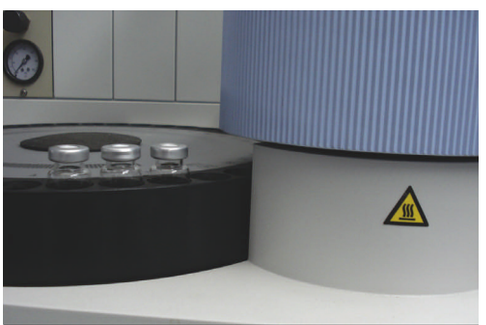
Nealie Newberger,
Crystal3 Laboratories

Contract manufacturers need to comply with the USP Monograph <467> to enhance their credibility and value on the global market.

It is probably safe to say that Asia's role in global pharmaceutical outsourcing remains optimistic despite the on-going issues with quality. How that role is going to continue evolving however, depends on suppliers' desire to become among those who will "rise to the occasion," in a market where cost may no longer be the primary motivator.

Learning from Experience

Key quality events in the past few years have had far-reaching effects that were felt across multiple continents, according to G Harris, *New York Times*, Apr 22, 2008. Western countries have repeatedly experienced contamination in not only toys and food products (for both human and animal consumption), but also in pharmaceutical raw materials, as reported by the US Food and Drug Administration (FDA), "Melamine Contamination in China", 2009; and "Pet Food Recall", 2008. However, most major pharmaceutical organizations admit that as part of their global intention to expand and reduce cost, the use of external international partners is still a requirement, according to *Pharm Tech* 33(1), 2009.



GC Headspace – a typical set-up for <467> testing. (Source: Nealie Newberger)

Drug Manufacturing

GC Headspace vials and standards for <467>. (Source: Nealie Newberger)

Pharmaceutical companies have heard the complaints of consumers and those of angry regulatory agencies. These companies and are actively moving to put into place an infrastructure which will control the quality of the companies they work with on an international scale – particularly in Asia. In an effort to balance risk and outstanding market opportunity, many of the larger pharmaceutical companies are looking toward compiling a network of suppliers, manufacturers and external partners that they will work with over the coming years. These companies are more likely to outsource to those that have been approved within the quality network.

This initiative provides an opportunity for external partners that are looking to acquire a piece of the outsourcing puzzle from these pharmaceutical companies. One of the most recent and far reaching issues facing pharmaceutical products today, as well as over-the-counter (OTC) products, is the United States Pharmacopeia (USP) Monograph <467> Residual Solvents Testing requirements.

Despite being staged to become effective in 2007, the complexity of the monograph's scope and debate among the scientific community, as well as the panel of experts at USP, delayed this chapter's arrival until just this past year. Many companies are simply not prepared to be compliant despite the notice given by regulatory agencies.

Ensuring Compliance

The implications of USP <467> are global and widespread to say the least. As pharmaceutical companies are trying to get up to speed with the regulations (harmonized and similar to those listed in ICH guidelines Q3C and EP guidelines), they must recognize that these requirements also apply to suppliers, manufacturers and New Drug Applications (NDA) / Abridged New Drug Applications (ANDA) holders.

Raw material suppliers and manufacturers need to be able to provide a certain amount of residual solvent (RS) information to their customers so that the purchaser may determine if the components meet the permitted daily exposures (PDE) requirements listed in <467> and ascertain if/what further RS testing is necessary. Anyone involved in pharmaceuticals (NDA/ANDA) must be compliant. However, the responsibility to ensure compliance ultimately lands on the owner of the NDA or ANDA. In the case of OTC and veterinary products, <467> does not apply, although ICH Q3C often does and with respect to RS are fairly equal in requirements.

Many trade journals state that pharmaceutical companies must go above and beyond the government's standards and ensure their own standards of quality, according to *Contract Pharma* 1(7), 2008. If raw material suppliers and manufacturers can anticipate the needs of their potential customers and provide this information in a forthcoming manner, it reduces the sting of these additional testing requirements and the burden placed on the NDA/ANDA holder.

Raising Productivity

This can improve release testing and overall turn-around times and ultimately lower the cost to the parent company. Once a vendor has been adequately qualified – it must still be re-qualified on a regular basis as deemed prudent.

External partners adhering to a strict quality testing regime that regularly and reliably provides data to the purchasing company, demonstrates a desire to be a better supplier. It also shows a commitment to excellence that can be appreciated by potential customers while ensuring the return of existing ones.

While these additional steps may be tedious at the beginning, they can be carried out fairly easily and routinely at minimal cost, after implementation. As potential and existing customers are presented with this valuable data, a few key deliverables can be expected:

1. A platform to demonstrate consistent quality in a product can be created and shared between the purchasing and external partner, ensuring an overall commitment to excellence and quality;

2. The purchasing relationship is fortified and hopefully continued over a long period of time;

3. Expenses can be saved on both sides during the partnership as the customer validates the vendor's process/data, reducing unnecessary testing.

Providing USP monograph <467> data is one way of becoming a more valuable vendor. The monograph uses specific wording and requires that testing be performed only for solvents "likely to be present." If the solvent is used or produced in the final manufacturing stages; or if it is used in previous stages and not removed by a validated method; or if it is contained in some of the starting material and not removed during the process, then RS testing must be performed, as reported by Pharmacopeial Education, Feb 12, 2009.

For additional guidance, the US Food and Drug Administration (FDA) has also published a Draft Guidance, as well a Question and Answer summary for RS and ANDAs. As the FDA is first concerned with patient safety, questions pertaining to RS testing should be directed to the administration.

Once it has been determined that testing is required; and the type of testing that needs to be performed, the monograph lists two options for establishing the amounts of RS in a product, assuming a 10g/day dosage according to USP/NF, 2009:

- **Option 1:** allows each component of a product to meet a concentration criteria (ie, less than the ppm specified);
- **Option 2:** allows for acceptance criteria based upon a Permitted Daily Exposure (PDE) limit (ie, daily exposure is calculated as the sum of the components in mg).

By performing this testing ahead of time, a supplier can determine RS information in ppm or in mg (daily exposure) and be ready to provide the data to the buyer upon its purchase of the material of interest. This quality initiative simplifies the process for all parties involved and provides the platform for building lasting quality relationships in global pharmaceutical outsourcing. **PA**

Enquiry code: 093E06

The Role of Bioinformatics in Biomarker Discovery

Tze Chuen Lee,
Writer

Bioinformatics provides a means of identifying biomarkers with greater accuracy.

When the microarray (the platform used by IVDMIA) was first introduced into research laboratories, it opened the path to revolutionalize research and to bring the world a step closer towards personalized medicine. A decade later, this dream became closer to reality when the US Food and Drug Administration (FDA) approved Agendia's Mammaprint in 2007 for its use to assess the risk of recurrence in breast cancer patients.

According to FDA, the medical device known as the In Vitro Diagnostic Multivariate Index Assay (IVDMIA) utilizes multivariate data (expression levels of several genes), and an algorithm to predict a single patient's clinical outcome. The algorithm usually involves the analysis of a correlation between the expression levels of a given set of genes, and the generation of scores that will eventually be used to classify the patient.

The derivation of the result (a black-box process) cannot be independently verified by end users (physicians).

Bioinformatics plays a key role in this analysis and forms the framework behind this black-box process. However, there is still no clear winner among the myriad of bioinformatics methodologies used to select the set of genes that are most predictive for the clinical outcome of a complex disease. Why is this so?

Difficulties in Microarray Analysis

The advent of the microarray poses challenges to bioinformatics. Careful considerations on the experimental design have to be made before any valid conclusions can be derived from the millions of expression values that a set of experiments typically generates. The existence of different microarray platforms offered by commercial and independent research groups along with the data formats that each possesses also adds complexity to their analysis. There are several approaches to normalize the expression data against the background, the control and the measurements of non-specific hybridizations.

Methods to reduce the dimensionality of the data into a smaller, clinically meaningful set of genes often needs a compromise between retaining genes that correlate to the clinical outcome of the disease and those that correlate to the observed clinical outcome by chance. All transcripts in the sample preparation are assumed to be unbiased in their hybridization to the probe. The effect this has on the expression values of subsets of the genes however remains to be examined.

Flaws in Techniques

Cluster analysis, statistical analysis, machine-learning, pathway signal analysis and the construction of interaction maps are approaches that bioinformatics specialists use. These are performed to reduce the dimensionality of the several thousand genes to a much smaller subset of genes (biomarkers) that meaningfully classify patients into clinically relevant subgroups.

Early experimental setups drew conclusions based on a relatively small number of patient samples. Although these early studies demonstrated that their set of biomarkers passed stringent statistical tests, their biomarkers often failed to correctly classify a separate, larger group of patients.

This was either because the markers worked only for a small subgroup of patients or that the markers were a result of chance due to fluctuations in the levels of expressions of the chosen genes.

As sample sizes get larger, more sophisticated machine-learning techniques have to be employed to correctly classify patients into their clinically relevant subgroups. In order to achieve their experimental goals, these machine-learning strategies often run into the mistake of causing too many samples to be used to train the machine. Too few test samples are also left over to sufficiently validate the technique.

Finding robust sets of genes that can accurately predict the clinical outcome of large groups of patients has been the main goal of scientists

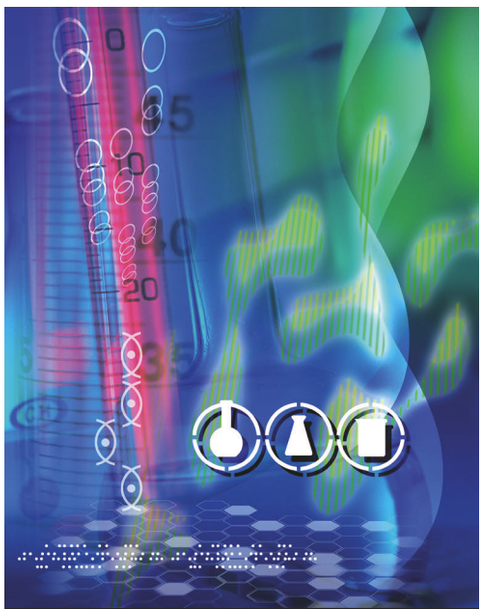
As a result, the biomarker candidates from various independent research laboratories working on similar experiments rarely produce the same biomarkers. And many of these biomarkers have unknown functions and effects on the clinical parameter in concern.

Various laboratories have come up with their own favorite sets of biomarkers. Hence, finding robust sets of genes that can accurately predict the clinical outcome of large groups of patients has been the main goal of scientists.

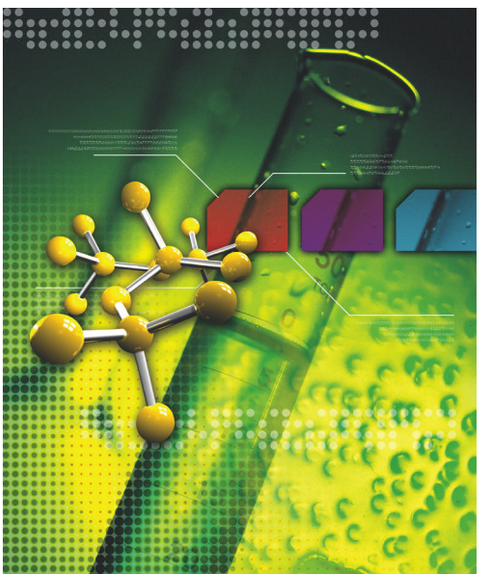
Accuracy in Prediction

Using genes of unknown functions in medical diagnostics can be a source of concern. About a quarter of the 70 genes used by Mammaprint to predict a disease outcome are genes

Drug Discovery



More studies are validating their biomarkers with a larger group of test sets and verifying them with publicly available datasets



Careful considerations on the experimental design have to be made before any valid conclusions can be derived from the millions of expression values that a set of experiments typically generates

of unknown function. However, this technology was shown to predict the 10-year survival of breast cancer patients at an accuracy level of 96.7 percent. A few follow-up studies have since supported its predictive power for patients' responses to neoadjuvant chemotherapy.

So has Mammaprint found the final set of biomarkers that best predict breast cancer patient survival and their responses to drug therapy? The study by Ein-Dor as described in Bioinformatics, 2005, investigated this set of 70 genes and found that there are many other sets of genes that can predict equally well especially when a substantial portion of these genes are correlated with patient survival.

Hence with a different subgroup of patients, these 70 genes may not perform as well as the prediction that was made on the original set of patients where they were first derived. There is a need to characterize these genes of unknown function, validate them using a much larger patient group and perhaps replace them with genes that will have a stronger predictive power when tested on a different subgroup of patients.

The biological mechanisms that function between the observed clinical outcomes and the set of biomarkers being discovered are generally not well understood. In the past where molecular biologists did not have to work with high-throughput data, conclusions were made from experiments where an observable effect on an experimental system were certainly due to its treatment, ie, a direct cause and effect relationship.

The mathematics, statistics, computational and engineering techniques required to process high-throughput data have been too much for most biologists to handle and the latter were left with little choice but to leave them to the "experts". Very often, these "experts" come from mathematics, statistics, computational sciences, physics or engineering backgrounds and may not possess the biological insights to perform the optimal procedures that are biologically meaningful to the data.

The techniques and procedures applied to the high-throughput data may be statistically acceptable and bioinformatically reasonable but may not be biologically optimal. For example, in microarray analysis, multiple hypothesis tests are conducted for each of the genes. Hence, the incorrect rejection of a null hypothesis is more likely when multiple testing is conducted.

In the process of reducing this error from multiple testing, genes that may be important for a given clinical observation may be removed from the statistical procedure simply because of some natural fluctuations in their expression levels in a subgroup of patients. Therefore, other approaches that manage to retain these important sets of genes while removing genes that by chance alone have significant scores, will be favorable.

Trends for Microarray-Based Biomarker Discovery

Relevant publications have adopted pathway-based methods and have used different types of interaction maps to provide greater biological insights into discovered markers. More studies are validating their biomarkers with a larger group of test sets and verifying them with publicly available datasets. The performances of these sets of genes from more recent experiments were shown to be relatively accurate in predicting the clinical outcome of a few hundred patients.

To date, thousands of biomarkers for various diseases have been documented in literature. It will be ideal to have a platform to analyze, share, categorize and score these biomarkers according to their potential of becoming clinically useful. However, heterogeneous data formats and the diversity of platforms have limited the interoperability of such systems. Conflicts of interests and competition between research scientists in getting their own set of genes into the clinic have also stifled the potential of such collaborative data-warehouses.

The sets of biomarkers that have emerged from various experiments are being validated in larger groups of patients. Pathway analysis and other biological relevant analysis are increasingly being conducted to understand the biological significance of the candidate biomarkers. If this trend should continue, perhaps in the next 5 to 10 years from now, we may reach a stage of understanding of the biological mechanisms behind some of these clinically useful biomarkers and how they affect various subgroups of patients.

Poor experimental design, heterogeneity of samples, weak methodologies in data collection and the lack of synergism in data analysis have been the key reasons of hampered progress in this field. There is a need to learn from these mistakes to improve the quality of future investigations. The positive results and feedback that Mammaprint has received so far has been promising and motivating.

It has in a way set the stage for a fiercer race toward getting the next IVDMIA into the market and hopefully, it could be one successful chip that takes a leap towards making personalized medicine a reality.

The next few generations of this assay have important roles to play in the future of human health. They must to do a good job in stratifying the patients accurately and providing greater biological insights into the relationships between their markers and the disease phenotypes that they are set to measure. And it looks likely that bioinformatics will continue to play a key and important role in making this a reality. **PA**

Enquiry code: 093E07

ISPE SINGAPORE CONFERENCE

IN ASSOCIATION WITH INTERPHEX ASIA 2009

To be held from May 31 to June 2, the event will a feature a host of speakers who will cover topics on the regulation, trends and opportunities in the Asian pharmaceuticals industry.

ISPE Singapore Conference 2009 will be held from May 31 to June 2 at Suntec Singapore. The conference will provide the region's regulatory agencies with an opportunity to discuss issues related to the adoption of regulatory principles and harmonization.

A key highlight of the conference is where participants will be provided with an opportunity to visit one of eight pharmaceutical manufacturing facilities located in Singapore, namely, GSK, MSD, Pfizer, Schering-Plough, Novartis, Genentech, Abbott and Lonza.

The event is co-organized by ISPE (International Society of Pharmaceutical Engineering) and Reed Exhibitions, with the aim of educating and advancing the region's pharmaceutical manufacturing professionals and their industry.

Under the theme of "Advancing Excellence and Innovation in Regional Pharmaceutical Manufacturing", the event will feature workshops, plenary keynotes and nine breakout track sessions. More than 35 industry speakers will share practical insights and updates on the global pharmaceutical manufacturing industry, and provide regulatory updates on key issues. They will also share their experiences on topics related to sustainable solutions, contract manufacturing, secondary pharmaceutical manufacturing and validation issues.

Speakers interviewed share their views on the opportunities, challenges and trends in the pharmaceutical industry in Asia. Excerpts on the following pages. **PA**

Show Report

Declan Lynch,
Operations Manager,
Zenith Technologies
Singapore

The Need for Automation

Where the end user is a global multinational company, there is usually a high level of automation deployed on its projects both in terms of R&D and manufacturing. This stems from the fact that it has already proven the automation case in other parts of the world and would most likely have established automation standards globally. The smaller, non-global pharma companies posses a lower level of automation but are quickly catching up with technology.

The demand for higher levels of automation is primarily based around the full batch sequencing of product manufacturing in a drive towards constant quality and reliability. Additionally, electronic batch recording and MES (manufacturing execution system) solutions are also technology areas that are experiencing increasing demand.

These solutions allow the establishment of fully integrated plants for the long term collection and storage of production information, and for the management of manufacturing resources. These resources include inventory records, product specifications, workflow management, and laboratory information.

The implementation of these technologies provides the link from plant management to business processes such as logistics, finance and sales. Many companies are now looking to automate these areas to provide greater visibility into overall plant management. **PA**

David Vincent,
CEO,
Validation Technologies

Validation Requirements that Affect Asia

In recent years, an increasing number of manufacturing facilities for active pharmaceutical ingredients (APIs) have relocated to Asia. Approximately 80 percent of the APIs used in the US and the European Union (EU) to manufacture finished pharmaceutical products come from Asia, with China and India accounting for much of the supply.

Asian API and drug manufacturers can better understand how they can achieve regulatory compliance and avoid production stoppages and recalls by following the guidance issued by the US Food and Drug Administration (FDA) and the European regulatory agencies.

The US regulator has published a document titled "Process Validation: General Principles and Practices," in order to help manufacturers maintain consistent quality and to improve efficiency. This document was also written to help the industry to understand the FDA expectation related to the validated state of each company they inspect.

The aim of these documents is to help both the US and international manufacturers to produce drugs more efficiently. This should help to lower costs and prevent shortages of critical medicines due to manufacturing failures and poor validation strategies that can result in product seizures and recalls.

However, this document is not intended to create new requirements for pharmaceutical manufacturing that go beyond those established in current regulations, nor is it intended to be a guide for the conduct of FDA inspections.

The European Medicines Agency (EMEA) and the FDA are faced with the daunting task of tackling the escalating problem of inspecting all API and pharmaceutical manufacturing sites in Asia.

There has been an accelerating rate of change within the industry over the last 20 years, with massive globalization driven by the pressure to bring drug manufacturing costs down. However, both the FDA and the EU have been focusing heavily on the validated state of these industries. They are inspecting compliance to current good manufacturing practices (cGMP) and the overall validation strategies within these companies.

The future is likely to see greater expectations and regulatory oversight related to validation goals and strategies for drug and API manufacturers. **PA**

Tony Uhe,
Senior Director Quality Operation,
External Manufacturing Asia Pacific, GPSG,
Johnson & Johnson

Growing Importance of Contract Manufacturing

Contract manufacturing in Asia Pacific is an area of growing interest. It focuses on supplying emerging markets and serves as a low-cost location for global manufacturing.

The region is "growing up" – where there was previously less scrutiny as sales revenues were small, there is now a greater focus on the region's strategic and financial value by senior management. This has resulted in increased resources being invested in the region to manage contract manufacturing.

A number of companies are using contract manufacturing to build up their production capacities. There is a growing pool of professionals in the industry and increasingly capable contract manufacturers.

There are however, challenges to be overcome. Protectionist measures exist that hinder manufacturing and/or testing, besides an increasing number of regulatory hurdles and trade barriers. The growing trend in counterfeits is causing problems for the industry and regulators by increasing costs and putting patients at risk. With the current global economic environment, it is difficult to obtain capital, resulting in a greater focus on keeping costs down.

Current trends in the region include an observance of higher standards in quality, safety and environmental impact. Supply chains are also becoming leaner. There is a need to build closer partnerships between multi-national corporations (MNC) and contract manufacturers. **PA**

Optimizing Energy Usage

Many companies may have the understanding that achieving a reduction in energy consumption lies in optimizing air conditioning operating hours, switching off unused equipment or looking for new technology to increase the efficiency of equipment.

However, a plan is required to execute all the energy conservation initiatives. Actions to reduce energy usage and improve equipment efficiency are just a part of the plan. One should consider the areas of ownership in the use of energy. There is a need to measure the actual usage so as to identify and prevent potential and actual energy wastage. It is also necessary to constantly seek technology and carry out resources planning to determine the approach to implement these initiatives.

Engaging staff to support the energy conservation initiative is equally important. The goal cannot be achieved if only a part of the organization working on it.

Yeo Yee Pang,
Energy Manager,
GSK

The drive to reduce energy wastage and achieve optimization should be sustainable. Any progress made should not be allowed to be easily reversed. While this may sound simple in theory, reversals are likely to happen if the majority of staff reject the changes.

There are advantages in sharing best practices within the pharmaceutical industry. If production plants have similar configurations, the technologies applied can be easily adopted from one plant to another without having to reinvent the wheel. **PA**

Sia Chong Hock,
Division Director,
Manufacturing & Quality Audit Division,
Health Products Regulation Group,
Health Sciences Authority

ASEAN Cooperation

The 10 member states of the Association of South East Asian Nations (ASEAN) have agreed on a Mutual Recognition Arrangement (MRA) on the Good Manufacturing Practice (GMP) inspection of manufacturers of medicinal products. This is via the Pharmaceutical Inspection Co-operation Scheme (PIC/S) GMP inspection system, as the benchmark.

The scope of this inspection covers all drug products in finished dosage forms, but excludes biopharmaceuticals, radiopharmaceuticals, traditional medicines and investigational medicinal products. Under this MRA, a listed (ASEAN) inspection service will have its inspection reports and GMP certificates, in respect of a medicinal products manufacturing facility in its territory, recognized and accepted by all other member States.

For an ASEAN inspection service to be listed under this MRA, the inspectorate must operate a PIC/S-equivalent GMP inspection system. The implementation date for this MRA is targeted for January 1, 2011.

Globalization and international pharmaceutical developments pose challenges to the regulator and the industry. Both have to embrace the constant changes and challenges that come along. No regulator can work in isolation in a globalized world. Collaboration via regional and multi-lateral agreements and other "work-sharing" programs seems to be the most appropriate strategic direction for regulatory agencies.

From an industry perspective, conformance to international regulatory standards and best practices appears to be the way forward in meeting the regulatory requirements of both domestic and export markets. **PA**

Prof Paul Sharratt,
Head, Process Science and Modelling Research Programme,
ICES

Benefiting from Continuous Processing

Improvement in pharmaceuticals manufacturing is a major worldwide trend. Whether the aim is reduced cost, increased production or tighter process control, many approaches are available.

New manufacturing technologies offer longer term improvements and are most easily implemented on new projects. Much attention is being paid to continuous processing in both primary and secondary manufacture. This gives the possibility of much tighter control of product quality. Viable continuous equipment is commercially available for a range of processing duties, while ISPE and others have been working on implementation and validation issues that arise as a result of the switch from batch to continuous.

The potential benefits of continuous processing are always case-specific, but may include increased reaction yields, more efficient separations, reduced processing times, reduced inventory, increased safety and reduced waste.

A better understanding of the process can also contribute to productivity. Not only does it reduce the number of failed batches, it can also be used to support improvements in processing efficiency. Increasingly, we can move away from the mindset of "change nothing – you don't know what might happen". Better understanding partly arises through the more effective use of sophisticated analytical techniques, allowing visibility into what was previously unseen either in the laboratory or on the plant (with process analytical techniques).

There also is a need to handle greater volumes of data, so techniques like the Britest toolset (for managing process understanding) and advanced statistical techniques are spreading rapidly. Methodologies like Six Sigma and Lean Manufacturing are being imported from other sectors, and these too bring significant benefits. **PA**

Show Report

Jacques Morenas,
Assistant Director, French Agency for the Safety of Health Products (AFSSAPS)/ Chairman, PIC/S

Enforcing Standards

The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) is an informal arrangement between 36 international authorities, in charge of regulatory inspections – mainly in the field of Good Manufacturing Practice (GMP) inspections for active pharmaceutical ingredients (API) and medicinal products.

Competent authorities from all the continents participate in PIC/S activities. Standards developed by PIC/S are similar to European standards and are recognized at an international level.

Participation in the scheme is the assurance for the local authority to have access to, to share and to participate in the elaboration of international standards in the field of inspections.

For pharma manufacturers in Asia's emerging markets, it is one way of being informed about and involved in (through local authorities and international associations of professionals) the globalization of the rules dedicated to API and medicinal products. It is an opportunity for speaking a common language and for understanding the expectations coming from major western authorities, in order to decrease the number of inspections. **PA**

David Drew ,
Group Pharmaceutical Director, Matcon

Lean Manufacturing – Continuous or Batch?

In order to increase productivity, the pharmaceutical industry needs to apply Lean Manufacturing philosophies as developed by high volume, multi-product industries with flexible production requirements.

Lean terminology like 'manufacturing to order', 'pull production', 'value stream mapping', 'reduction of inventory', 'just-in-time production', 'work flow,' and 'sweat the asset' are now widely used in the industry.

The real-time product release (on a continuous or batch basis) using Process Analytical Technology (PAT) is now a commonly accepted concept and seen as the key factor in enabling a production line approach to pharmaceutical manufacturing.

However a misconception is for 'continuous monitoring' to be understood as 'continuous processing', which then means 'continuous manufacturing'. This is not the case in high volume, multi-product industries where 'workflow' and not 'process' is recognized as key to achieving Lean Manufacturing.

The definition of 'workflow' in a modern car plant where every car is made-to-order with different colors, engines, upholstery and wheels etc, is that a car can be considered to be: "A batch of components, manufactured in parallel and assembled together in a continuous timely manner". That is, continuous production on a batch basis.

Whether the process is actually continuous or batch should be evaluated only on its ability to be part of a Lean Manufacturing concept:

- Can it keep up with the average pace of production?
- Can it provide flexible processing / production?
- Does it provide the lowest average cost of production (per kg, per day)?
- Does it produce the least waste?
- Does it achieve the required quality on all products?

The pharmaceutical industry already has a number of processes, which by their nature, can be considered as continuous. They are: dry granulation/roller compaction, hot melt extrusion granulation (both of which also reduce granulation costs), sieving/milling, tablet compression, capsule filling, sachet filling and blister packaging.

Other processes that are being developed for continuous processing include: mixing wet granulation and tablet coating.

The critical component in achieving the workflow for Lean Manufacturing in the pharmaceutical industry is efficient, flexible material handling. This is the missing link in achieving parallel manufacturing and processing. Whether the process is continuous or batch is of secondary importance. **PA**

Dr Prasad Kanneganti,
Director of Technology, Genentech Singapore

Efficient Analysis

One new technology that is fast becoming popular for the analysis of pharmaceuticals is RRLC (Rapid Response Liquid Chromatography) or UPLC (Ultra Pressure Chromatography) methodology. This replaces the conventional HPLC (High Pressure Liquid Chromatography) methodology typically used for the assay of drug substances and impurity profiling.

Several analytical equipment manufacturers now offer this option. RRLC/UPLC equipment is priced slightly higher than conventional HPLC. However, low operating costs, testing speed and agility more than compensate for this. Conventional HPLC methods can be run on RRLC/UPLC equipment, making the latter suitable for both new and existing methods.

The latter offers several advantages over conventional HPLC. It offers higher sensitivity and component separation is achieved faster without losing resolution. Chromatographic columns used are packed with smaller diameter particles, and require pressure range of 8000 to 14000 psi. A shorter run time means lower solvent usage, contributing towards the operation of a 'Green Laboratory'.

From a regulatory filing viewpoint, RRLC/UPLC is based on the same principles as HPLC and hence the demonstration of equivalence is easier. Modification of the chromatographic conditions and changes to sample preparation are generally required. It is recommended to use the same type of column/packing material with the exception of the particle size and column dimensions. Using the same detector also simplifies method validation and effort to demonstrate equivalency.

Several vendors also offer assistance for the conversion of conventional methods to rapid methods. Spreadsheets are used to translate conventional HPLC parameters to RRLC/UPLC parameters. A fivefold decrease in run time is not uncommon. As a start, rapid methodology for in-process testing and non-regulatory methods such as those used for the analysis of plant cleaning samples is recommended. The experience gained is useful for developing more complex methods such as assay testing. **PA**

Enquiry code: 093E08

Product Focus
Cell Culture/Imaging

Enhancing Single-Cell Gene Expression

The Fluidigm 48.48 Dynamic Array provides an efficient solution for single cell gene expression quantification studies using off-the-shelf TaqMan Polymerase Chain Reaction (PCR) assays and reagents.

The technique is used with the BioMark System to produce inexpensive and easily reproduced gene expression results from single cell samples.

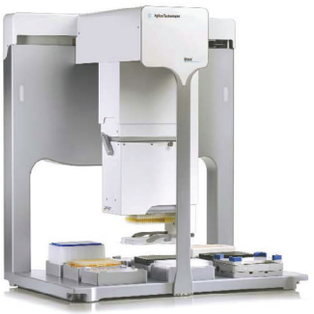
The key to this technology is the matrix of channels, chambers, and valves in the array that does the work of assembling assays. Using the product, scientists can have the same quantitative PCR (qPCR) data quality and experiment flexibility that they are currently receiving from a 384-well system while increasing throughput by 24 times.

To run an experiment, 48 samples and 48 assays are loaded into the inlets of the dynamic array input frame and pressure loaded into 2,304 reaction chambers. Using this approach, scientists are able to test 48 genes against 48 samples in a single run.

A 2,000-sample study that can be completed with 4,032 pipetting steps using the array would require 192,000 steps to complete using microplates.

Fluidigm, www.fluidigm.com
Enquiry code: 093P01

Isolation of Total RNA



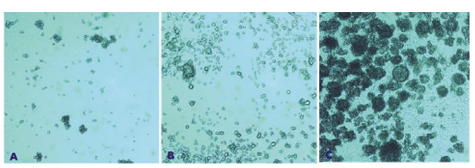
Agilent Automation Solutions has released a technical note. It describes an automated method for the isolation of total ribonucleic acid (RNA) in a 96-well format using the Bravo Automated Liquid Handling Platform and the Absolutely RNA96 Microprep Kit from Strategene.

The kit allows the high throughput isolation of total RNA from small samples of cultured cells. This method eliminates toxic phenol-chloroform extractions and time-consuming ethanol precipitations by selectively binding RNA from cell lysate on 96-well silica fibre matrix plates. However the RNA isolation protocol requires extensive manual processing including repetitive pipetting, washing, vacuum filtration and centrifugation steps.

Using Agilent's VWorks Automation Control Software, a script was written for the liquid handling platform to aspirate, dispense, mix and transfer samples from a source 96-well tissue culture plate to the binding and collection plates of the RNA 96 kit. The script also automates sample wash steps by using a vacuum filtration unit accessory on the platform. The platform's space-saving nine plate-position footprint can fit inside a standard laminar flow hood, enabling automated liquid handling for cell-based assays or hazardous reagent handling. Additionally, its open design permits access from all sides for integration with other devices and standalone use.

Agilent, www.agilent.com
Enquiry code: 093P02

Three-Dimensional Cell Culture



Sigma offers its first human Extracellular Matrix (ECM), MaxGel, and HydroMatrix synthetic peptide. These products create 3D cell culture environments in which stem cells and other types of cells are better able to resemble and behave like their *in vivo* counterparts.

A challenge in culturing stem cells is that many cell-based assays used in research and screening laboratories are not representative of complex *in vivo* cellular behavior – because they are not being performed in *in vivo* like environments. It is now possible for cell-based systems to progress by switching from two-dimensional (2D) to three-dimensional (3D) environments in vitro, in which cells are grown and studied.

Unlike growing cells on 2D flat surfaces, cells in a 3D environment behave and respond more like they would *in vivo* to internal and external stimuli. This stimuli includes changes in temperature, pH, nutrients absorption, transport, and differentiation. The power of regenerative medicine provides the means to understanding cellular progressions such as development, aging, and tissue rejuvenation. A way to understand these processes is to study model systems that resemble those in the organism.

Sigma-Aldrich, www.sigmaaldrich.com
Enquiry code: 093P03

Hepatocyte Isolation System

Most traditional methods published for isolating hepatocytes use partially purified enzyme preparations, including various types of collagenase and other proteases. The use of better characterized preparations of collagenase such as Worthington Types 1 and 4 (CLS-1, 4) provide better results, according to the company.

Crude collagenase preparations can contain lot-variable contaminating proteases, esterases and other enzymes, requiring researchers to pre-screen several lots of enzyme and/or continually modify isolation parameters and protocols. The Worthington Hepatocyte Isolation System has been developed to provide researchers with a convenient and consistent hepatocyte cell isolation system. By using the pre-optimized combination of enzymes contained in this kit, it is possible to minimize the lot-to-lot variation and improve the quality of the isolated hepatocytes.

The reagents are stable at ambient temperatures for the periods of time expected in normal shipping procedures. Contents may be stored at 2-8°C for 4-6 months before use. The package contains sufficient materials for five separate adult rat liver perfusions.

Worthington, www.worthington-biochem.com
Enquiry code: 093P04

Calendar of Events

May 11 – 12, 2009
Site Management for Clinical Trial
Singapore
www.marcusevans.com/html/eventdetail.asp?eventID=15325&SectorID=31

May 12 – 13, 2009
DxRx Summit: Nucleic Acid Diagnostics & Therapeutics Summit
Boston, US
www.selectbiosciences.com

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

May 14 – 15, 2009
RNAi World Congress
Boston, US
www.selectbiosciences.com

May 14 – 15, 2009
Intelligent Lean Laboratories
Singapore
www.marcusevans.com/html/eventdetail.asp?eventID=15284&SectorID=31

May 31 – Jun 2, 2009
ISPE Singapore Conference
Singapore
www.ISPESingaporeConference.com

Jun 1 – 2, 2009
INTERPHEX Asia
Singapore
www.interphexasia.com

Jun 1 – 3, 2009
Drug Discovery & Development Japan 2009
Tokyo, Japan
www.ibclifesciences.com/japan

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

Jun 5, 2009
18th International Seminar on Global Clinical Trial Management and Pharmaceutical R&D
China, Beijing
www.worldcourier.com/seminar/cn/beijing.html

Jun 8 – 9, 2009
EuroPLX 40
Warsaw, Poland
www.europlx.com

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

Jun 15 -16, 2009
Clinical Partnerships Asia 2009
Mumbai, India
www.ibc-asia.com/CRO

Jun 15 -19, 2009
2009 PDA/FDA Asia Pacific Pharmaceutical Ingredient Supply Chain Conference
Shanghai, China
www.pda.org/asiapacific

Jun 16 – 17, 2009
Medico-Legal
Kuala Lumpur, Malaysia
www.abf-asia.com/project/9551MC_PA.pdf

Jun 17 – 20, 2009
PROPAK Asia 2009
Bangkok, Thailand
www.propakasia.com

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

Jun 23 – 25, 2009
CPhI China 2009
Shanghai, China
www.cphi-china.com/content/default.aspx

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

Jun 29 – 30, 2009
BioPharm Asia
Singapore
www.ibc-asia.com/biopharmasia

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

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

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

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- Commissioning & Qualification
- Auditing for GMP

9 Industry Breakout Tracks on 1 & 2 June 2009, Monday & Tuesday

- Regulatory
- Sustainable Solutions
- Secondary Pharma
- Manufacturing Excellence
- Automation
- Contract Manufacturing
- PIC/S Regulatory Update for Emerging Markets
- BioPharma
- Validation: Hot Topics

Pharmaceutical Facility Visits on 3 June 2009, Wednesday

- Abbott Nutritional Manufacturing Facility *New*
- Genentech SG Product Operations Facility *New*
- GSK – Production Bldg 2 & R&D Pilot Plant
- Lonza II Bulk Bio Facility *New*
- Merck Sharpe & Dohme API & Tablet Plants
- Novartis Solid Dosage Manufacturing Facility
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