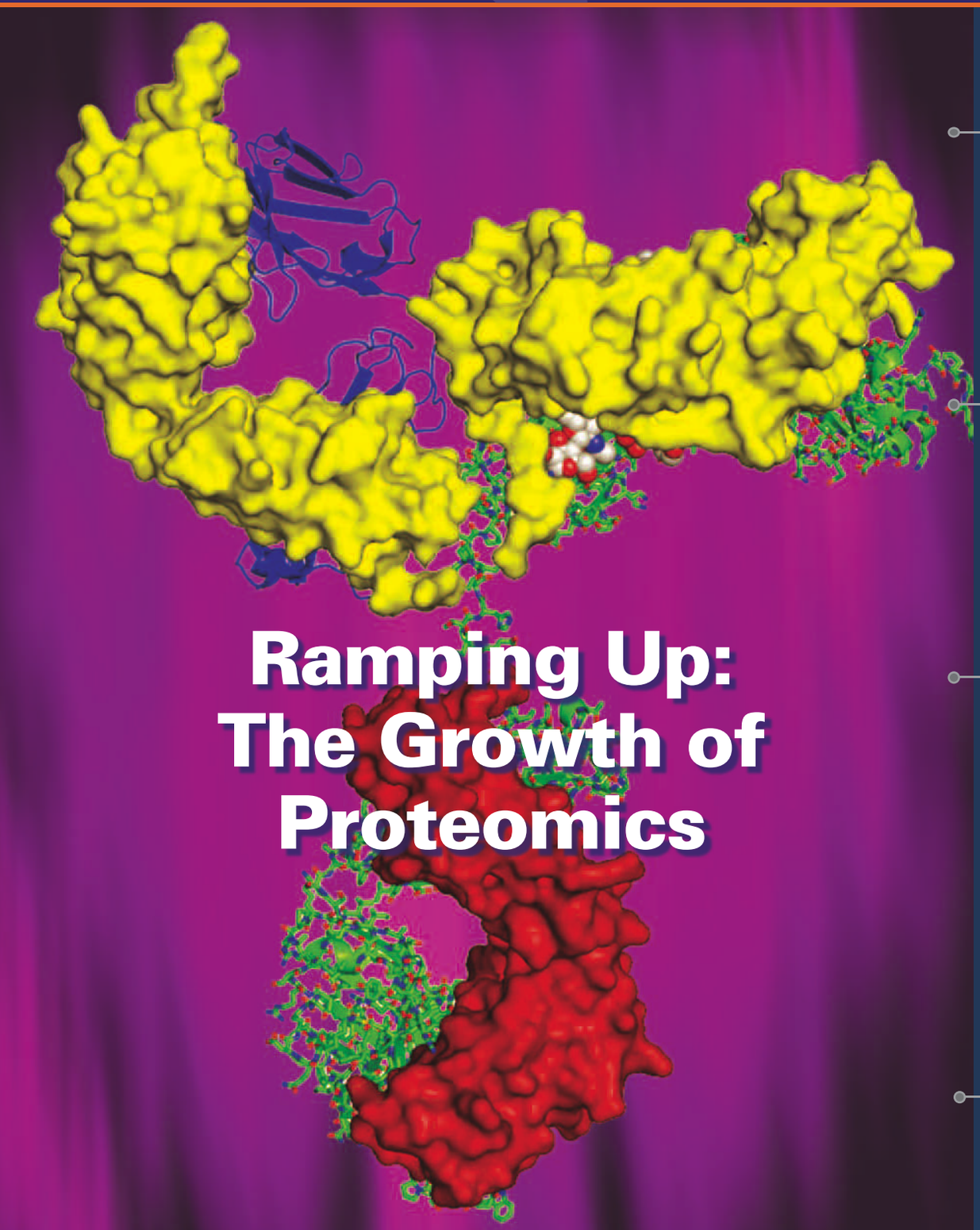
Reed Business Information

www.PharmaAsia.com
NOVEMBER-DECEMBER 2009

PharmaAsia Digital

A leading resource for the pharmaceutical industry



Ramping Up: The Growth of Proteomics

Drug Delivery

Software-as-a-Service in Cold Chain Traceability

Drug Development

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

Drug Discovery

Animal-Free Solutions for Biopharmaceuticals

Electroporation: Transfecting Primary Cells

Regulatory & Compliance

Global Compliance with Analytical Method Validation

THE UHPLC DEBATE IS OVER.

The NEW Agilent 1290 Infinity LC

Infinitely better.

The Agilent 1290 Infinity LC is the last word in ultra high-performance liquid chromatography (UHPLC). Period. It delivers the infinite power range, enabling you to deploy any particle type, any column dimensions, or any mobile and stationary phases. It's what you've always wanted: a single system that provides infinite capabilities to solve all your analytical challenges in HPLC, LC/MS and UHPLC. For resolution, sensitivity and speed that are infinitely better, the choice is clear: the Agilent 1290 Infinity LC. **We'll prove it at www.agilent.com/chem/infinity**

Our measure is your success.

Agilent Technologies

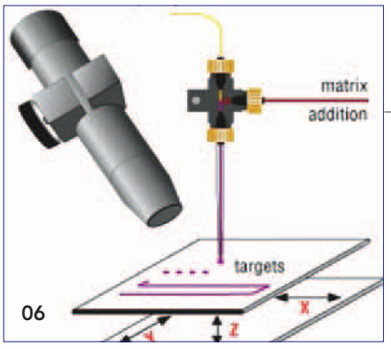
Reed Business Information

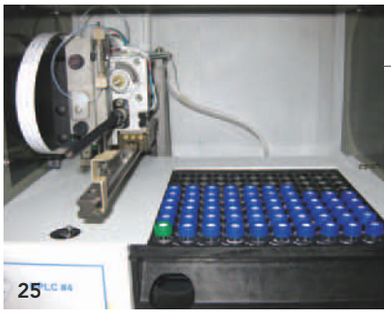
www.PharmaAsia.com

PharmaAsia Digital
A leading resource for the pharmaceutical industry

November-December 2009

Contents





Cover: Courtesy of Proteomics International

PharmaAsia is published eight times a year by Reed Business Information Asia, located at The Signature, 51 Changi Business Park Central 2, #07-01, Singapore 486066. PharmaAsia Volume 4, Number 8.

Editor's Note

Michael Tham
Editor

Survival of the Fittest

It's been a challenging year and for some, the not-so-habitable landscape may have forced an exit from the playing arena.

However, for others who have managed to survive the trials of 2009, many have emerged fitter. PPD, a global Contract Research Organization (CRO) has completed its acquisition of BioDuro – a Chinese drug discovery outsourcing company. With nearly 1,000 employees under its payroll in China, PPD claims that it is now the largest CRO to offer clinical development and discovery services in the country.

Similarly, IDBS, a provider of research data management and analytics solutions to R&D organizations, has also expanded its operations in Asia with the opening of offices in China and Australia.

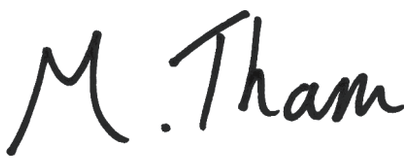
Market expansion is also taking place in the "online" space. Sigma-Aldrich has launched a life science-based application for the social media site, Facebook. The "What's Your Favorite Gene?" application is designed to encourage collaboration and networking, and allows scientists to share their own experiences on the genes that drive their research.

Moving further down the value chain, the launch of Pharmatching.com, a B2B website, is helping to match demand and supply in services outsourcing, and of active pharmaceutical ingredients.

There are also some who have undertaken the road to "quality improvement". World Courier for one, has announced that it now meets the standards for Good Practice (GxP)–compliant status. With this system in place, the company adheres to industry requirements for the management of time- and temperature-sensitive clinical trial materials.

At country level, Singapore is the first non-Organization for Economic Co-operation and Development (OECD) member in Asia to achieve the OECD- Mutual Acceptance of Data framework (MAD) status. This development is expected to attract greater numbers of biomedical and pharmaceutical companies to conduct their testing activities in the country.

As the year draws to a close, our team at *PharmaAsia* would like to thank our audience for their continued support. We would also like to take the opportunity to wish everyone a merry Christmas and a very prosperous New Year! **PA**



PharmaAsia Digital
A leading resource for the pharmaceutical industry

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

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

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

SALES & MARKETING
Regional Sales Manager
Alvin Lim, (65) 6780 4521; alvin.lim@rbi-asia.com
Marketing Executive
Laura Low, (65) 6780 4302; laura.low@rbi-asia.com
Ad Admin Executive
Cyndi Yap, (65) 6780 4816; cyndi.yap@rbi-asia.com

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

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

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

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

Reed Business Information

REED BUSINESS INFORMATION ASIA
The Signature, 51 Changi Business Park Central 2,
#07-01, Singapore 486066
Tel (65) 6789 9900 Fax (65) 6544 1221
www.PharmaAsia.com

Big Pharma Seeks to Insulate Itself from the "Patent Cliff"

As the pharmaceutical industry moves closer towards the 'patent cliff', Big Pharma is implementing strategies to lessen the impact of the loss of patent protection on some of the industry's biggest sellers on their collective bottom lines.

In an effort to mitigate the impact, Big Pharma is seemingly investing time and energy into diversification. However, a report by Datamonitor suggests that diversifying away from the core business of developing prescription drugs is not the cure to the pending ails of the patent cliff.

Key patent expiries within the pharmaceutical sector will intensify from 2011 onwards, affecting some of the biggest brands in the industry, such as Pfizer's Lipitor (atorvastatin), driving down revenue growth for pharmaceutical companies.

Between 2001 and 2008, the collective revenues of Big Pharma companies grew by 8.6 percent year-on-year. If this rate of growth was maintained, revenues would have reached US$628 billion in 2014. However, revenue growth amongst Big Pharma will flat-line at 0.2 percent between 2008 and 2014, leading to forecasted sales of US$387 billion in 2014.

This slow-down in revenue growth is almost entirely attributable to the expiration of patents for key products; a phenomenon from which few within the Big Pharma peer-set will emerge unscathed. Therefore, the question is on how to deal with the forecast decline in revenue growth, leading some companies to consider diversifying away from the branded pharmaceuticals sector.

The pharmaceutical business model is currently undergoing major change, as the industry seeks to maximize operational efficiencies, driven both by the current economic climate and the patent cliff, says Datamonitor pharmaceutical strategy analyst Dr Pam Narang. "Although these changes might provide a cushion of sorts to the forecast decline in revenue growth for Big Pharma, a more aggressive response is required, and diversification away from pharmaceuticals is one avenue that a number of companies have pursued."

Branded pharmaceuticals represent just one sector within the healthcare landscape. While pharmaceuticals has historically been the most popular single merger and acquisition (M&A) target sector for Big Pharma, it is notable that "ex-pharmaceutical" sectors were collectively responsible for just under half (47 percent) of all acquisitions undertaken between 2000 and Q2 2009.

The different sectors pharma can and have diversified into, include over-the-counter healthcare products, medical devices and diagnostics, animal health, retail pharmacy and health insurance.

Although Big Pharma could potentially off-set sales growth decline by diversification, the resulting fall in operating margin would act to reduce operating profit and somewhat negate the benefits of diversification. Therefore, pharma-focused companies have little to gain from diversifying away from branded pharmaceuticals, and should instead "ride out" the patent cliff by looking to increase operating margin.

While cost-cutting and restructuring can go some way to achieving this goal, merging with and acquiring other pharma companies and biotechs to gain access to their drug development pipelines is a more powerful means of improving operating margin; somewhat justifying the clutch of mega-mergers that Big Pharma have historically entered into. **PA**

Ergonex Pharma Receives Award from Frost & Sullivan

Ergonex Pharma has received the "European Orphan Diseases Entrepreneurial Company Award" at the Frost & Sullivan's 2009 Excellence in Healthcare Awards Banquet, held in London, UK. The award was presented to the company in recognition of its innovative therapeutic concept, its display of technological know-how and targeted vision.

Ergonex Pharma is focused on the clinical development and commercialization of Terguride for the treatment of distinct orphan diseases. The drug is currently being evaluated for the treatment of Pulmonary Arterial Hypertension (PAH) in a Phase II trial in Europe and results are expected in 2010. **PA**

Exco InTouch Opens Global Headquarters in the UK

Exco InTouch has opened a global headquarters at the historic Pishiobury House, Hertfordshire, UK. The move to the larger premises will allow the company to continue its growth with plans to add to its team over the next six months. The HQ will house the project management, IT, sales and marketing, accounting and general management teams. The main IT platform will remain at a secure location in the UK with a similar site in Raleigh-Durham, North Carolina, US. **PA**

Actavis: Launch of Cholesterol Drug in Spain

Actavis Group has announced that its third-party sales division, Medis, has delivered 30 million tablets of Atorvastatin to its clients in Spain. This is the first generic version of the blockbuster molecule to reach the Spanish market, according to the company.

The drug efficiently regulates the blood cholesterol levels and is used in the therapy of primary hypercholesterolemia. It is produced by Actavis in 10mg, 20mg and 40mg tablets. **PA**

Regional News

Roche Opens Biologics Manufacturing Site in Asia Pacific

Roche has held the dedication ceremony for its biologics manufacturing site in Singapore at the Tuas Biomedical Park.

The fully-owned subsidiary is established in Singapore under the name Roche Singapore Technical Operations. With a combined investment of approximately US$500 million, the site is comprised of two facilities which use two different production technology platforms to manufacture biologic medicines. Currently employing approximately 330 highly-skilled workers, the facilities occupy approximately 12.6 hectares.

L-R: Dr Franz Humer, Chairman of the Board of Directors of Roche; Tharman Shanmugaratnam, Minister for Finance; Jörg Reding, Swiss Ambassador to Singapore; Dr Patrick Yang, Executive VP, Genentech Technical Operations; Balkis Jamil, Biotechnologist, Roche Singapore Technical Operations; Jim Miller, VP and GM, Roche Singapore Technical Operations; Carmen Ong, Biotechnologist, Roche Singapore Technical Operations

The site marks the company's first biologics manufacturing presence in the Asia Pacific region. Roche Singapore Technical Operations is expected to be the first company in Singapore to produce licensed biotherapeutics using recombinant Deoxyribonucleic Acid (DNA) technologies.

Dr Patrick Yang, executive VP, Genentech Technical Operations, who will assume the role of Head of Global Technical Operations of Roche Pharma in January 2010, stated, "As we supply a global market, Singapore offers important advantages to our manufacturing network, including a skilled labor pool, nearby biotechnology expertise and a supportive business environment."

One of the two facilities manufactures biotherapeutics that are derived from bacterial cell cultures and is to produce Lucentis (ranibizumab injection). The facility is expected to receive US Food and Drug Administration (FDA) licensure in the first half of 2010. Designed as a multi-product facility with a fermentation capacity of 1,000 litres, the 12,000 sq meter single-storey facility is capable of producing other bacterial products in the future.

The second facility will produce medicines using mammalian cell cultures. The facility will manufacture Avastin (bevacizumab), a targeted cancer therapy which provides survival benefits across multiple tumor types such as colorectal cancer, lung cancer, breast cancer, brain cancer and renal cell carcinoma. The building is expected to receive US FDA licensure for production of Avastin in the fourth quarter of 2010.

With 80,000 liters of production capacity, the 27,000 sq meter facility has future plans to manufacture Herceptin (trastuzumab), a humanized monoclonal antibody which is established as the foundation of care for patients with HER2-positive breast cancer. **PA**

Quintiles Opens Asia Pacific HQ in Singapore

Quintiles, a fully integrated biopharmaceutical services company offering clinical, commercial, consulting and capital solutions, has announced the opening of its expanded regional headquarters facility in Singapore's Science Park I.

Dr Dennis Gillings, Quintiles Chairman and CEO

Encompassing three floors of Science Park's Cintech IV building, the regional headquarters facility doubles the size of its previous space in Singapore and provides additional room for expansion as future demand grows.

Quintiles is leasing a total of 79,000 sq feet (7,300 sq meters) of space, capable of accommodating approximately 550 employees when fully occupied. In addition to variety of regional and clinical functional groups, the facility is also home to a central laboratory facility. The 13,000 sq foot (1,200 sq meters) central laboratory facility doubles the size of its previous lab in Singapore. The expanded lab facility provides a variety of globally harmonized lab services and plans are already underway to expand these capabilities with the addition of an Assay Development Lab (ADL) and an anatomic pathology lab. **PA**

Hyphens Reaches Distribution Agreement with Indonesian Companies

Hyphens Marketing & Technical Services has announced the signing of a distribution agreement with Nicholas Laboratories Indonesia and Kebayoran Pharma.

Under the terms of the agreement, the former which already has a registered representative office in Indonesia, will be responsible for sales and marketing. Nicholas Laboratories Indonesia will seek regulatory approvals of various products from The National Agency of Drug and Food Control (BPOM) Indonesia. Kebayoran will be responsible for the nationwide distribution of goods. **PA**

Ramping Up

Advancements in instrumentation, computing power and drug discovery techniques are fuelling the growth of proteomics.

Dr Richard Lipscombe,
MD
Proteomics International

Proteomics promised much when it was first conceived in the late 1990s as the protein equivalent of genomics. Although its initial hype and a lack of practicable realism dented early expectations, technology and expertise have surged forward in the last few years. Diverse applications have emerged from drug discovery to biosimilars, and biomarkers to sophisticated protein chemistry.

What is proteomics? It can be defined as "the analysis of proteins on an industrial scale." Protein chemistry has moved from a meticulous and relatively slow science to a high-throughput, full scale development in biology and the role played in it by proteins. In the process, proteomics has moved from the bench top to spawn an industry of its own, in fact more than one, and these have consequences for the pharmaceutical industry.

Growing Importance

With its maturation, proteomics has moved to play a complementary role to that of genomics. Deoxyribonucleic Acid (DNA) sequencing, gene mapping, transcriptomics, micro arrays – these are all critical techniques that serve to supplement the depth of biological data that is available in the protein world. Without genomics and the advances in computational capability under the heading "bioinformatics", proteomics would not have been likely to move out of its 1990s depression.

The latest developments in proteomics reflect the broad and growing number of techniques that come under the proteomics banner. This is because proteins are both the operational and functional molecules of life. In colloquial terms, DNA provides the recipe, but proteins are the meal.

The formal definition of proteomics is the "analysis of all the proteins in a cell, tissue or organism, or more simply, a system." Exemplifying the practical term of system, proteomics is used narrowly to study specific pathways within a cell, or broadly, with the example of the Brain proteome project centered in Germany, to map every protein that is involved in the operation of the most complex organ on the planet.

There is also the sub-proteome containing all the peptides in a system – the peptidome – a rapidly growing area of interest in the biotechnology industry. Proteomics has evolved to become more than just identifying a protein.

Most developments in proteomics have focused on a systems approach, and specifically system comparison and biomarker discovery. Applications range from human diseases such as cancer and diabetes, to salt tolerance and pathogen resistance in crops. This is achieved by comparative proteomics that use techniques such as chemical labeling directly into the mass spectrometer, or variations on traditional Two-Dimensional gel Electrophoresis (2DE) with fluorescent tags.

The first step in any system is to map the proteome and to obtain maximal protein coverage – and there are many ways to achieve this. The original mapping technique of 2DE is visual. It remains a cost-effective approach and is a technique that small laboratories can utilize.

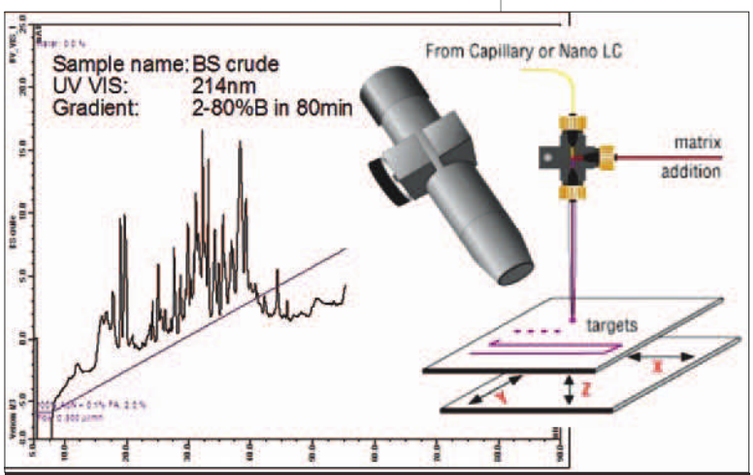
Its weakness has always been reproducibility, with replicates of 3-5 gels being necessary to achieve quality results. These replicate gels are then combined into a master image,

Cover Story

which has been made possible by software tools such as Progenesis, and these images are compared between samples. Proteins that are identified as changing in concentration with statistical significance can then be excised, (enzymatically digested into peptide fragments) and identified by mass spectrometry.

Key improvements in reproducibility have arisen with the use of fluorescent tags and plastic backed gels. The former, which can be exemplified by Differential in Gel Electrophoresis (DIGE), allows two samples that are labeled with different chromophores to be analyzed simultaneously on a single gel – providing savings in time, although specialist imaging equipment is required.

The fear that the precious gel could still tear and results be ruined, appears to have been overcome when GelCompany introduced durable and fluorescence compatible plastic backed gels. The remaining weakness of 2DE is low throughput coupled with its non-automatable nature, which has led to the growth of comparative analysis directly by mass spectrometry.



Proteome analysis has gained speed with the use of LC-MALDI, whereby eluates from an HPLC column are mixed with matrix and spotted on to a target for high-throughput MALDI-TOF mass spectrometry. (Source: Proteomics International)

Advancement of Technology

Instrumentation is the other key component to the reawakening of proteomics. The developments in mass spectrometry hardware have been impressive and it is difficult to find an instrument that will not serve a proteomics laboratory well. This has created a multi-million dollar industry that is illustrated by the US$1.1 billion acquisition of MDS Sciex/Applied Biosystems by Danaher.

The major manufacturers have enabled the sensitive mapping of many protein and peptide systems – 50 micrograms of protein extract from a cell culture can be sufficient to identify over 1000 proteins from that system, or a single scorpion sting can be mapped to identify over 300 new peptides.

The range of mass spectrometry instruments is vast, but is centered on two core ionization techniques – Matrix Assisted Laser Desorption Ionization (MALDI) and ESI (Electrospray Ionization), followed by a mass measurement device, popularly ion traps, and Time-Of-Flight (TOF).

Many instruments produce complementary protein identification results. The rule of thumb is that for a given system, MALDI will yield 50 percent of the proteins, and ESI 50 percent, with 25 percent common to each, while 25 percent of the proteins may never be seen. In any system, more sample will always improve the number of protein hits. However, the fundamental physico-chemical properties of proteins and peptides means that some molecules simply cannot be detected (eg, they do not ionize or are insoluble).

For any particular application, it is a matter of selecting high-throughput or precision, and innovative hybrid instruments which combine different principles that allow enough variation in mass spectrometer types to suit the needs of a proteomics facility.

As recently as ten years ago, it was standard practice to identify one protein in 24 hours with Edman N-terminal protein sequencing. It is now possible to sequence and reliably identify one protein in one minute with a mass spectrometer. This was the start of the first transformation of protein chemistry into proteomics.

High-Throughput Processing

Gigabytes of genetic data, sophisticated computing power, broader expertise and innovation have since propelled this forward. Built on the diversity of the mass spectrometers, a range of modular approaches have been combined to increase the efficiency and depth of proteome mapping.

In particular, High Performance Liquid Chromatography (HPLC) has taken over 2D gels as the method of choice for sample separation. Some of the most successful techniques are based on the Multidimensional Protein Identification Technology (MudPIT) approach, which uses a series of chromatography steps (usually ion exchange and reverse phase) to separate a complex mixture of protein fragments.

An essential step is that the entire protein sample is first digested into peptides, before it is applied to the HPLC. This ultimately presents a bioinformatics challenge, but saves time because the sample (ie, all the peptides) can be directly analyzed by mass spectrometry.

In order to compare the differential protein expression of two or more samples, the proteins from each source can be chemically and uniquely labeled before the separation experiment begins. Two popular techniques are iTRAQ, which can be used to compare eight tissue samples simultaneously, and SILAC, an isotopic method that is readily incorporated into cell culture media.

In these scenarios, the peptides are identified and simultaneously quantified, with the tags being used to indicate relative protein amounts. An alternative option to labeling is direct spectral counting whereby the intensity of each peptide ion is measured in the mass spectrometer, and this value is used for quantification. When successful, the comparative analysis produces new information on the key components of the system – biomarkers for that disease or trait.

The objective of current developments is to improve peptide separation and sensitivity, without producing so many fractions that the mass spectrometer is then occupied for weeks on end. The initial approach was ESI-MS, with the direct injection of HPLC eluates into the mass spectrometer.

This has the immediate advantage over the 2D gel approach where proteins are both separated and identified in the process. There is the contrast however, that while proteins in a 2D gel that is stained with Coomassie blue dye can be excised and analyzed months later, HPLC protein fractions require prompt analysis because their stability is limited in this form.

Another development has been the advent of LC-MALDI mass spectrometry, whereby the HPLC eluates are mixed with matrix and are simultaneously spotted onto MALDI targets. This has a number of advantages: firstly, high-throughput TOF/TOF instruments can be used to process the samples; second, the samples are stable on the target and can be archived, to be processed at a convenient time; and third, the samples can be re-analyzed.

There is a degree of complementarity between LC-MALDI and ESI-MS, because each will identify different proteins, but the efficiency of LC-MALDI is giving it the impetus.

The coverage that is obtained by the different proteome mapping methods varies. However, there appears to be an emerging trend, which is reflected in the comparable analysis of heart systems that obtained approximately1000 (rabbit) proteins by LC-MALDI, approximately 650 (rat) by MudPIT LC/MS/MS and 375 (human) by 2D-gel electrophoresis. However, no one approach will tell the entire story.

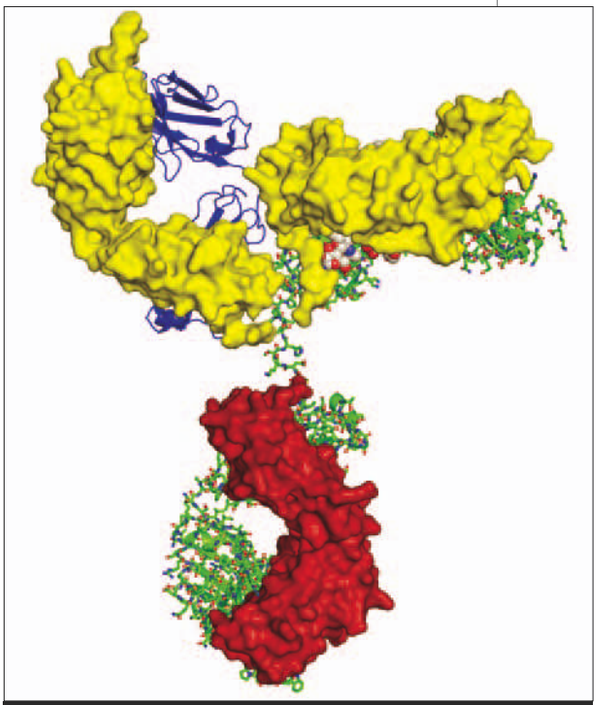
Whichever system is used, vast amounts of data are created – one comparative proteome mapping experiment today can create a file that is nearly one gigabyte in size. This requires computing power and necessitates centralized super computers that can handle the data of many groups. The Australian Proteomics Computational Facility is one such example, which accepts data from any group in the Asia Pacific region.

Drug Discovery

The power of LC-MALDI and other related techniques for proteome mining also opens doors for the pharmaceutical industry – a means of discovering new drugs from natural products.

Using traditional screening techniques, venom has already been proven to be a source of peptide drugs with multi-million dollar blockbusters such as captopril (Brazilian Viper),

exanatide (Gila Monster), and ziconotide (Cone Shell). By adapting sensitive proteome mapping techniques and combining bioinformatics tools, an entire venom such as that of the black scorpion can be analyzed, enabling new molecules to be identified, synthesized and their activities tested.



(Source: Proteomics International)

In particular, the peptidome fragment of the proteome is an obvious target, since it hits both the sweet spot of the mass spectrometer, and the (current) optimal deliverable size range of protein drugs. To emphasize this, the peptide market is growing twice as fast as overall pharmaceuticals, with a market size in 2007 that is estimated at over US$3 billion with a projected growth rate of more than 10 percent per year.

In the same year, there were 67 therapeutic peptides on the market, 150 in clinical phases, 400 in advanced preclinical phases, and globally over 100 pharmaceutical and biotech companies that were active in peptides. These were achieved with traditional approaches.

Encompassed in the study of single pathways is the need to fully understand the actions of each entity, and an essential component is Post Translational Modifications (PTMs) – with phosphorylation being the prime example. The use of specialist instruments such as Applied Biosystems' 4000Q hybrid ion-trap or Thermo's Orbitrap have made the dissection of signaling pathways a reality. Major pharmaceutical companies are spending several million dollars in this pursuit. Notably, cell signaling is not restricted to phosphorylation alone, and other mechanisms such as sulphonation and redox changes of thiol groups are gaining traction. Studies of such PTMs are unfolding using current proteomics technology.

A spin-off from this interest has been to open the door to all aspects of protein chemistry, and to provide a suite of tools for the emerging biosimilars market. This represents one of the most understated elements of proteomics – utilizing its power as a precision approach for the quality control of biosimilars.

This growing market is forecast to be worth between US$19 billion within five years according to MarketsandMarkets, and US$77 billion within 2 years, according to RNCOS. Biosimilars, also termed biogenerics or follow-on biologics, represent second generation versions of blockbuster biologic products. Biosimilars are expected to have a profound impact on all aspects of the pharmaceutical industry.

Monoclonal antibody type drugs are the biggest sellers, with demand for novel medications like insulin, beta interferon, G-CSF and coagulation factors growing considerably. The European Union and the US have some of the most advanced biosimilars sectors while Japan, Canada, Australia, and particularly India and China are upcoming significant players.

Complete molecular characterization, from the verification of amino acid sequences to disulphide bridging and the ratification of PEGylation sites is emerging. Many techniques remain in their infancy in traditional analytical labs, whilst accredited facilities are rare.

Agencies such as the US Food and Drug Administration (FDA) are starting to realize the power of this era of proteomics, and are pressing for reliable mass spectrometry-based data. Regional testing authorities such as National Association of Testing Authorities (NATA) in Australia, and Asia Pacific Laboratory Accreditation Cooperation (APLAC) are responding. It is probable that ISO/IEC 17025 laboratory standards will become an essential Quality Control (QC) requirement for advanced proteomics facilities.

Proteomics has become more than just a single protein identification method. With the engagement of the other 'omics platforms – genomics, transcriptomics, bioinformatics and metabolomics – today's scientists have a breadth of complementary techniques at their fingertips. **PA**

Enquiry code: 098E01

Software-as-a-Service in Cold Chain Traceability

Software-as-a-Service that incorporates Instant Messaging (IM) concepts, aids in the monitoring and control of perishable products in transit.

Bernard Lee,
MD, Procuro Asia Pacific

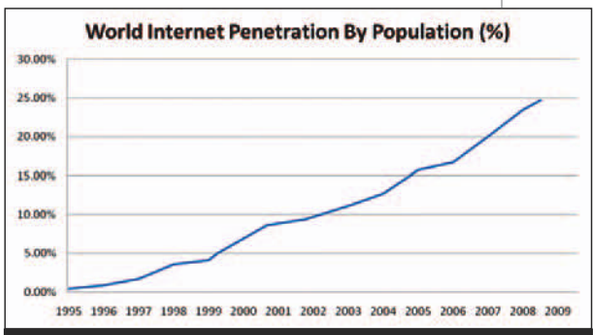
Cold chain breaks often occur in demarcation points between different business entities. The prevention from such breakage has traditionally been the reliance on the careful selection of business partners, immaculate operational management, best practices and well-executed auditing.

With the explosive growth of worldwide connectivity, it is now not only possible, but also practical to apply in-time or real-time, end-to-end monitoring to cold chain shipments. The resulting information that is gathered, allows the adaptation of true rule-based management by exception techniques towards cold chain compliance management – and when processed, can provide trend, grading and compliance reports.

Paradigm Shift in IT through Connectivity

During the past decade, the world had seen advances in Internet connectivity. Such advances have impacted various industries. One of the most significant influences was on the way that consumers make traveling and accommodation reservations.

Previously, consumers had to rely solely on travel agents equipped with dedicated mainframe terminals that were hooked up to various proprietary airline and hotel reservation systems. Today, consumers can independently make their bookings and reservations via the Web.



(Source : Internet World Stats)

The logistics industry has also experienced its share of influence by the Internet. Customers of courier companies have been using Internet based tracking for a while. By selectively providing access to operational information on the Internet, courier companies have allowed shippers, receivers, and other parties to have complete visibility on the progress of packages that are being delivered.

Up until recently, the cold chain logistics industry has not gained much benefit from the use of Information Technology (IT) and the Internet because of certain reasons. First, it involves a number of different organizations (compared to travel reservations or courier services). The sheer volume, diversity and meshed coverage of cold chain logistics preclude any single entity from providing end-to-end services.

Second, while a plane ticket and a hotel can be on the same reservation but remain totally uncorrelated, different entities that are participating in the same cold chain are intricately linked. Defining where the responsibility ends for one entity and where it begins on another is more an art than a science. The art form defies the nature of IT, which typically requires a well defined problem before a solution can be applied.

Many of the newer IT concepts that have only been introduced recently, are the key ingredients that can be used to overcome such difficulties which traditional IT wisdom fails to address. Thanks to the consumer adoption of connected desktop and handheld devices, marketing terminologies for these concepts are already in the vocabulary of many technology savvy managers.

Collaboration and Software-as-a-Service (SaaS)

A courier company can easily allow access to its tracking information through the Internet. In the cold chain logistics industry, it is inadequate even if every participating business makes available their own tracking and temperature information to other parties.

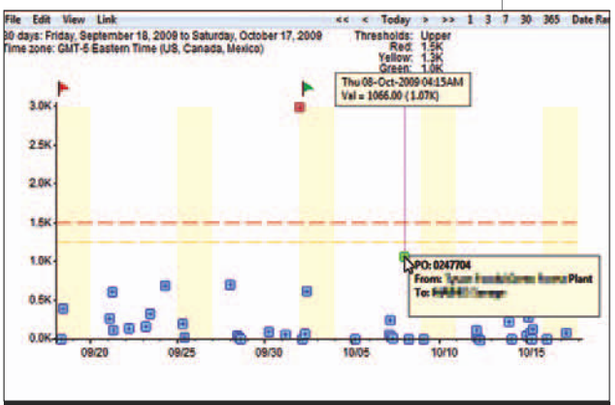
Electronic Data Interchange (EDI) and Service Oriented Architecture (SOA) have allowed IT systems from different companies to exchange information, but at a relatively high cost. With

Drug Delivery

Software-as-a-Service (SaaS), the service provider offers a specialized pay-per-use application. The user does not have to make expensive investments and it takes only a few minutes to sign up for an account online. This allows various business entities that are participating in a cold chain – large or small – to collaborate and benefit from the same system without the barriers of entry from EDI and SOA.

The use of email in the business environment had seen its share of problems in the last few years. The proliferation of email competes for users' limited attention and important messages may get "buried". With the widespread problem of unsolicited (spam) email, technology for junk mail filters has to be in place and constantly improved. However, important emails are sometimes accidentally dropped or rejected.

The concept of Instant Messaging (IM) is an example of human IT interaction design. It attempts to do less for users so that the latter has greater control. Using some of the IM concepts, rule-based management by exception techniques can be applied to cold chain compliance monitoring.



Shipment Quality Quantification and Visibility (Source: Procuro)

Issues which need real, immediate attention such as cold chain breaks can be delivered in the form of IM – and most important of all, grouped and presented in the way that the user is best able to consume and digest the information.

The concept of social networking can be applied to cold chain compliance management. Relationships among processing plants, carriers, distribution centers and end customers can be defined, once they become participants of the same SaaS. From the defined relationship, measurements can be made. For example, by mapping the relationships between all the participants in the same cold chain and associating the relationship to the serial numbers of temperature loggers being used, all parties will know where the logger is going and what exactly it is monitoring at any given time. Lost or undocked recorders can be tracked, and if a cold chain ever breaks during shipment, everyone will have full visibility on where and how the cold chain has been broken.

Auditing vs Total Visibility

Auditing and certification has been widely used as a yardstick to measure the quality of perishable products that are being delivered. While it is still one of the best yardsticks to measure a company's overall health, the cost of IT and connectivity has dropped to a point where it is now practical to track and store the temperature history of all shipments.

Once sufficient data has been gathered, the resulting data mining reports provide insights on what can be done to further improve operations on a management level.

The confidence level for future auditing and re-certification also increases with total visibility. Traditionally, the carrying out of well-defined operational procedures relies entirely on the people who are responsible for the execution. Without total visibility, the result of the audit is an educated guess until the audit is performed. With total visibility however, the result of the audit is already known before it takes place.

Pertaining to total visibility, one primary obstacle for its use would be costs of implementation. One of the hottest topics to date is the use of Radio Frequency Identification (RFID) enabled temperature loggers. While such solutions are readily available today, the industry is still waiting for another round product design breakthroughs:

1. While RFIDs alone are completely passive, adding a temperature logging function requires the presence of a built in battery. This drives the cost and size up, and the shelf life down. Patents for scavenging ambient energy sources already exist, but it may be at least a number of years before a viable product can be developed.

2. While most Enterprise Resource Planning (ERP) software already support RFID, the integration between RFID enabled temperature loggers and a company's existing Management Information System (MIS) applications remain a highly specialized and complex task. Temperature information, even after integration, remains as "Auxillary information", which means they are not available to the powerful reporting, trending and data mining features of today's ERP applications.

This is a chicken and egg problem. The early adopters will need to pay for the higher development costs, until the volume for the hardware and software integration lowers costs and vendor competition, and make the solutions affordable to mainstream users. This cycle has already been seen with traditional RFID and same is expected for RFID-enabled temperature loggers.

Better Utilization of Traditional Temperature Loggers

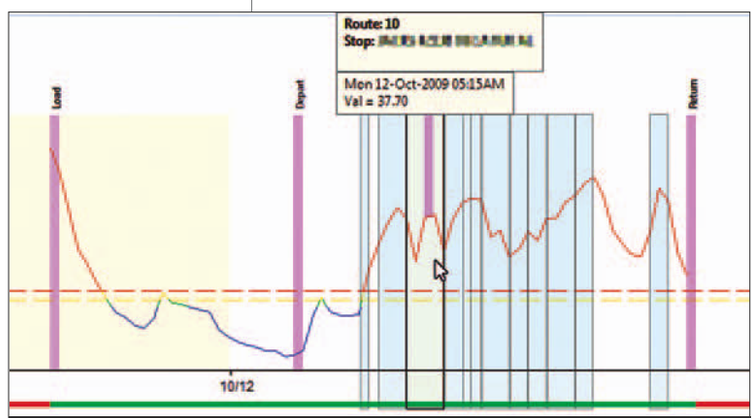
While waiting for the perfect solution, it is possible to obtain greater mileage without paying the hefty costs of bleeding edge technology and perfect integration – through the efficient use of software and internet connectivity.

With traditional temperature recording, the party who is responsible for receiving and accepting the perishable goods will download the temperature data, study the temperature charts, and decide whether or not the shipment is good or bad. While this one of the best and most accurate methods for individual shipment inspections, it is heavily dependent on individual judgment, and verification can only be performed via auditing at a much later date. The fast food industry has developed an effective way of quantifying thermal abuse, along with the concept of "thermal minutes."

The usable shelf life of a perishable product is directly related to its total exposure to thermal abuse. This can be calculated by multiplying the product's temperature difference with the expo-sure time for each sampling interval and then summing them up. Multiple shipments can then be quantified against the Y axis and plotted on the same chart.

The shipments which have been exposed to thermal abuse will stand out, and will automatically be flagged for acceptance or rejection.

This concept allows middle and senior management from all the parties that are participating in the cold chain to have total visibility on all shipments, while focusing only on the exceptions. This is so that time will be better spent on formulating management strategies for long-term improvement. The traditional use of temperature loggers involves repetitive procedures for downloading logged temperature data. Data can be manually saved for future reference. Recorded temperature charts can be printed out and physically attached to the shipment documentation for filing. With RFID enabled temperature loggers and ERP integration, the process can be significantly simplified, but at a relatively higher cost.



Delivery Events Overlay through use of GPS Geofencing. (Source: Procuro)

By connecting the interface cradles of traditional temperature loggers to a SaaS provider – similar to sending a package through a courier service, the destination, service level and carrier information are already defined at the time of shipment.

Simply plugging the temperature logger into a cradle at the reception site while being logged into the customer's SaaS account will acknowledge receipt (similar to the receiver of a courier package who signs for the delivery). The tracking information, together with the temperature history, will be automatically uploaded to the SaaS provider, where data analysis, compliance and trend reports will be generated in real time and made available to all participating entities that are authorized for viewing.

Delivery Tracking

All documents and packages that are shipped via a courier service are tracked for delivery confirmation. Through use of SaaS, traditional temperature loggers and therefore cold chain shipments can be tracked in a similar fashion, without the need for ERP integration.

Since the order, carrier and destination information are already registered with the SaaS provider prior to shipment, they will be marked as "outstanding" until the reception site docks the logger while being logged into an authorized account. With delivery tracking, users will be informed if the cold chain compliance information on any single shipment fails to enter the monitoring system – achieving the same level of confidence that is attainable with high-end RFID enabled logging systems with ERP integration.

Where Less is More

Sometimes it is better for a computer or a software to do less. Instant messaging is likened to having conversation. If Person A shouts to Person B from across the hall and Person B does not hear him, it is up to Person A to wait until Person B comes closer before calling out again. Person A does not expect anyone to repeat his calling if Person B does not hear him the first time.

IM, or IM related tools like twitter, focus on showing the current state of the people or things of concern. Is he Busy, Available, Bored, Happy, Out of town?

The nature of alerts focuses on what needs attention now. Receiving alerts via email is a widely accepted practice, but email by nature, is not suitable for receiving and managing alerts. IM and Twitter are more suited tool for this purpose – because by doing less, they do what they are supposed to do better. They simply show the user the current status of the things which need attention, and leave the handling of such information such as filing to the user.

For some forms of communication, email may be trying to do too much. When a sender sends out an email, he assumes that the recipient is going to read it. This is not necessarily the case. If the recipient does not read the email, it remains in the mailbox, assuming that the recipient will deal with it later.

If alerts are sent to a user's email account, they all remain inside the user's mailbox, regardless of whether the alerts are current or out-of-date. And then there is spam mail, spam filters, automatic filing, sorting, filtering etc, which try to help the user to organize his email account that is typically getting increasingly out of control.

Loose ERP integration techniques can be applied at a fraction of the cost of traditional ERP integration. The standard 80/20 rule for IT applies – identify and focus on 20 percent of the features that save 80 percent of human efforts, and leave the rest to humans.

By borrowing from IM and social networking technologies, each participating entity within the cold chain will have an account with the SaaS provider. Their relationships will be defined in a onetime effort. Critical operational information such as delivery schedules can be exported from the ERP system. This is adequate for taking cold chain visibility to the next level without imposing a barrier of entry due to costly implementation.

With loose ERP integration, location based services can also be used in a non-traditional way to provide valuable information for management decisions through rule-based exception reporting. With the use of proper Global Positioning System (GPS) hardware and the knowledge of GPS coordinates of all delivery locations ahead of time, it is possible to track arrival, delivery and departure times, predict future late deliveries, and prevent potential cold chain breaks due to unforeseen staff scheduling. Shipments requiring attention can then be cross referenced to temperatures in the trailers, cross-docks, cold stores and their respective loading and unloading times. The root cause of all occurred cold chain breaks can be analyzed for future improvements in cold chain handling.

Rule Based Management By Exception

Management by exception techniques allows managers to focus on the areas of business which truly require attention.

Rule based management by exception takes this concept one step further. Through the use of IT and the definition and automated calculation of key performance indicators, the management tool alerts the manager whenever the business operating parameters either meet or fall outside of predefined rules.

One major advantage of this technique is the reduced dependency on judgment calls by individual managers. For example, if a pharmaceutical shipment has been thermally abused, the receiving manager makes the call on whether or not the shipment should be rejected, typically after looking at a temperature chart of the duration of shipment.

By quantifying thermal abuse and pre-defining rules for shipment rejection based on product type, the management tool can mandate an inspection if the rules are met, and display the thresholds and rules that have been violated. These would then require the receiving manager to input the actions taken as well as the reasons for such actions.

Besides reducing dependence on individual judgment, this tool also helps with meeting regulatory compliance and auditing requirements. Rule based management by exception on cold chain compliance is most effective if the total visibility of every shipment is achieved.

While the use of temperature tags can prevent thermally abused pharmaceuticals from accidentally being accepted for administration to achieve full traceability of a damaged shipment, it is necessary to associate time and event information to the temperature recordings. Through the use of geo-fencing techniques and loose ERP integration, delivery routes are uploaded to the SaaS provider. An arrival, delivery or departure event along with the timestamp is logged when the GPS coordinates of a delivery truck coincides with those of a supplier, warehouse, cross dock or delivery location, or when a door is open.

The events and timestamps are then matched to the recorded temperature data on the delivery truck or the temperature logger. When an exception criteria is triggered, managers of all parties that are responsible for maintaining the cold chain integrity will know when and where the cold chain break has occurred.

It has been difficult previously, to apply IT to the cold chain logistics industry. In recent years, concepts on use of IT have been introduced to both the corporate and consumer markets. Such concepts can be adapted relatively easily to change the way that a cold chain is monitored and visualized. With end-to-end visibility in a cold chain, the art of quality assurance can now be carried out in an increasingly scientific approach. **PA**

Enquiry code: 098E02

Bernard Lee has designed and written software for companies such as Star TV, Microsoft, Union Bank of Switzerland, Hong Kong Trade Development Council and Cisco. He is a co-founder of Procuro and original architect of PIMM. PIMM is a SaaS provider for cold chain compliance and traceability monitoring for a number of quick service restaurants and their supply chains in the US and Europe.

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

India, China and Singapore each posses different strengths for pharma investments.

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

India, China and Singapore are in direct competition with Europe, the US and Japan where many pharmaceutical Multi-National Corporations (MNCs) are already well established in the latter countries.

For a Western company, the question of where to settle or invest, or to collaborate is often difficult to answer and depends on many factors. However, the answer often means that the company needs to be active in all three Asian countries.

Compare & Contrast

An attempt has been made to compare pros and cons of China, India and Singapore in general (Figure 4).

Country	India	China	Singapore
Strengths	• Low cost structure • Large naive patient population for clinical studies • Huge talent pool • Many FDA / EMEA approved API / drug product suppliers • Proximity to reputable API suppliers • Educated employees are English speaking • World-class chemical–pharmaceutical R&D capabilities	• Low cost structure • Western standard infrastructure in R&D hubs like Shanghai and Bejing • Huge naive patient population for clinical studies • Huge talent pool • Sufficient number of FDA/ EMEA approved suppliers • Biggest Asian pharma market besides Japan • Strong government support for pharmaceutical investments and R&D • Mainly well-established chemical R&D capabilities	• Low cost structure, mainly by tax incentives and subsidiaries for investors • Politically and economically stable • Positive image in all targeted markets • English speaking employees • IPR legislation
Weaknesses	• Weak infrastructure within the country • Long distance to targeted markets for any products • Re-analysis for any exports to EU/US • Low attractiveness for expatriates • Foreign drugs cannot be evaluated in First-Entry-Into-Humans (FIH) trials – can only be tested as of phase I beyond FIH • Job hopping	• Long distance to targeted markets for any products • High initial overhead costs in manufacturing and R&D • Many equipment suppliers still not present • Re-analysis for any exports to EU/US • Government bureaucracy language barrier • Enforcement of Intellectual Property Rights (IPR) legislation still an issue • Foreign drugs cannot be evaluated in phase I trials • View of GLP/GMP is not currently aligned with Western standards • Need for a broker or local facilitator to interface with Chinese companies and suppliers • Need to work with Chinese government to facilitate business processes • Job hopping	• Long distance to targeted markets for any products • Small local market • Re-analysis for any exports to EU/US • Competition for talent
Opportunities	• Worldwide hub for supply of pharmaceuticals • Growth potential of domestic market	• Worldwide hub for supply of pharmaceuticals • Growth potential of domestic market	• Preferred R&D hub in Asia • Synergies between Singapore based pharma companies
Threats	• Poor image for "Made in India" pharmaceutical products	• Poor image for "Made in China" pharmaceutical products • Political stability / relations towards important markets like the US or Japan	• Cost competitiveness mainly due to government measures • Limitations by lack of qualified local workforce

Figure 4: SWOT analysis for India, China and Singapore. (Source: Frank Floether)

Drug Development

Comparing only India and China, each country offers different advantages despite having general similarities. Both countries' capabilities are still not uniformly "world-class" across the R&D value chain. However, this may change in a few years.

Activity	India	China
Biology research	Few capabilities, evolving	Some capabilities, rapidly evolving
Chemistry research	Strong and proven capabilities	Good capabilities in basic services
Chemical & pharmaceutical full development	Strong experience in full GMP capabilities (chemical, formulation, analytical)	Limited to API development; chemical, formulation/analytical in full GMP still immature
Preclinical trials	Emerging capabilities, rapidly evolving	Emerging capabilities, evolving
Clinical trials	Fairly strong capabilities, fast growing	Strong capabilities, fast growing

Figure 5: India's and China's capabilities differ in certain R&D areas. (Source: Frank Floether)

Some of the best opportunities in both countries are chemistry–based activities and clinical trials. In terms of chemical activities, India has more complete services in CM&C (Chemistry, Manufacturing & Control), including formulation and analytical services, up to full development for international filings.

Typically, many Active Pharmaceutical Ingredients (API) companies in India do not have a significant understanding of biology and the management of microorganisms. Preclinical and biological capabilities are opportunities in both countries, with China outpacing India in innovative biology.

In general, China is stronger in biology and is rapidly improving its skills. It has been the only country in the developing world to participate in the International Human Genome Project. Through investments, Chinese companies can now produce hepatitis vaccines, recombinant insulin, interferon and other generic therapeutic biologics.

While India's biotechnology sector is growing rapidly, its emphasis is still on vaccine production and bio-services.

China is strong in fermentation technology. State investments have changed the landscape in China, thwarting Indian attempts to progress in bio-generics. India has lost out in the fermentation business, such as Pen G, 7-ACA etc, to China, also due to the latter's lower energy costs.

China has adopted large capacity expansion and has captured the global market with aggressive pricing. Power interruptions, which are common in India, are fatal for fermentation. Government support for pharmaceutical R&D in general is also comparatively stronger in China.

On the other hand, India has a broader vendor base (which is also directly accessible – often not the case in China), a workforce fluent in English and more effective IPR protection.

Indian companies have the strongest appetite for acquisitions and the least for divestments. About 48 percent of Indian companies are considering acquisitions compared to 31 percent in Singapore and just 17 percent of Chinese companies.

In contrast, 46 percent of Chinese companies and 44 percent of Singaporean companies are open to foreign investments in their companies compared to just 20 percent in India, according to PriceWaterhouseCoopers.

Protecting Intellectual Property

Firms in India and China are important suppliers of low–priced APIs and finished

products to international markets. A concern is that the introduction of product patents will adversely affect these industries and lead to an increase in drug prices in the importing countries.

However, the impact of the current patent regime is much broader: besides access to new medicines in India and China, changing IPR is influencing the business strategies of Indian and Chinese firms. It is providing an incentive for them to invest in R&D to improve their products and rankings in the marketplace.

IPR also affects Western MNCs that are operating in these countries. The IPR situation in China is still perceived as "tricky". MNCs are establishing or expanding their presence in China to allow themselves to test the conditions of the market and to build relationships for the future.

Many of the local engagements remain focused on discovery research activities, with an avoidance for projects that are considered "sensitive" from an IPR standpoint.

India still has a reputation of relatively weak IPR protection. However, pharma companies are now bringing more "sensitive" projects to India, indicating that there is growing confidence in the country.

While being perceived as an issue, IPR protection is a decreasing barrier to offshoring R&D activity. R&D activities like chemical and pharmaceutical development, are generally less affected.

Drug Development

To illustrate, up scaling and optimizing an API manufacturing process for a New Molecular Entity (NME), formulation development, analytical method development and validation as well as running analytical stability studies are all activities which typically happen in the later stages of the R&D process. This is after the patent protection of a new molecule has been completed.

With proper contractual agreements in place and the careful selection of a reputable vendor, IPR risks may be effectively managed. For major pharmaceutical firms (especially in India) that are working towards establishing themselves as significant players in the international pharma market, infringing on the intellectual properties of the customer will not be in the best interest of the service provider.

India has a more mature legal system for IPR protection than China, but significant practical issues still exist in both countries. While the risk for legal aspects such as the patent registration process, patent law coverage/protection and information disclosure requirements by customs/government in India is considered low, it is at least moderate in China.

The risk for practical aspects such as law enforcement/legal system efficacy and support of overall environment (IPR track record, governmental policy, business environment and culture) ranks moderate in India but high in China.

The Boston Consulting Group has summarized its findings in a study (Figure 6)

Subject	India	Rating	China	Rating
Patent registration process	• Filing requirements at par with US / EU	++++	• Long and complex process	
Law protection	• Same strength and application as in the UK • Both process and product protection under WTO agreement	++++	• Significant differences in "first to file" vs " first to use" • Laws are not always similarly applied to domestic and foreign companies	++
Law enforcement	• Litigation can be settled in courts in the EU	+++	• China's court system still struggles to handle IPR issues • Established patent training institutes for IPR administration	++
Culture / Government	• Historically lacks IPR protection • Significant improvements in recent years	++	• Traditional view of IPR as a common good • Government invests in public education	+
No. + = Least favourable —> ++++ = Most favourable				

Figure 6: IPR risk comparison between India and China. (Source: Boston Consulting Group)

Offshoring Clinical R&D

Globally, the clinical research outsourcing market was estimated by Merrill Lynch to be at US$12.3 billion in 2007. This market is expected to reach US$23.1 billion by 2011. The Indian clinical research market was estimated by Cygnus Industry Insight at US$200 million in 2007 against US$140 million in 2006, and a mere US$70-80 million in 2001-2002.

As of 2007, about 100,000 clinical trials were underway around the world, involving at least as many physician investigators and more than two million participants. This is a

substantial increase from a decade ago, when the number of trials was less than two thirds of this figure.

The increase can be attributed to several factors. For example, the increasing data requirements from regulators; greater use of lifecycle management such as indication expansion (requiring clinical tests); and the ongoing development utilization of data collection and management technologies that enable larger scale testing.

As the number of trials increases, their sizes are also growing. According to the US Food and Drug Administration (FDA), patient volumes have risen by about 25 percent from the early 1990s to about 4,500 volunteers per New Drug Application (NDA) in 2006. This increased size and volume translates directly into a greater need for more patients.

At the same time however, rising levels of consumer medication consumption are making it more difficult to identify potential study subjects who are not taking medicines that could interfere with the action of the drug that is under investigation.

The result is that clinical trial recruitment in the West now consumes about 30 percent of overall clinical trial time and up to 40 percent of clinical trial costs – more than any other activity associated with clinical testing.

MNCs have concerns about the escalating new drug development costs. Clinical trials now cost as much as US$5,000, US$6,500 and US$7,600 per patient for phase I, II and III respectively, according to Datamonitor in 2008.

This situation has led to the expectation that within the next two to three years, up to 65 percent of the studies that are regulated by FDA and sponsored by MNCs will be conducted outside the US, with Asia being a key destination.

Many researchers and pharmaceutical companies are beginning to look at China's and India's massive populations as an asset for clinical trials. Emerging diseases such as Severe Acute Respiratory Syndrome (SARS), and medical conditions that are particularly prevalent in China – such as diabetes and hepatitis – present an opportunity to make rapid advances in clinical research.

Furthermore, still relatively few Chinese and Indians have access to medicines (drug naive patients), which makes it more straightforward to test drugs without having to worry about interactions with other compounds. Meanwhile, the widely introduced Good Clinical Practice (GCP)/Good Laboratory Practice (GLP) guidelines and other Western regulations in most Asian countries are another pull factor.

As to the cost of clinical studies, testing in China is reported to be only one third of the cost of trials in the Western world. However, the downside is that Chinese regulators typically take as long as a year to grant companies permission to conduct clinical trials (compared with just two months in Singapore).

In regard to clinical trial capacity, there were 205 institutions that were accredited in China to conduct clinical studies as of 2006. The number of State Food and Drug Administration (SFDA) approved multinational clinical studies in China has also gone up from zero in 2002 to 53 in 2007.

There are however, some factors to consider in any offshoring decision. Drugs which are not already commercialized in any other country have to pass clinical tests from phase I to phase III in China.

In addition, if a drug has not passed phase I in another country, approval will not be given for conducting its clinical trials in China. Drugs which have already been marketed in a different country can skip phase I/II in China – but only if phase I/II had been carried out in East Asia (eg, South Korea or Japan) – otherwise a retesting may be required in China.

What about India? McKinsey estimates that by 2010, global pharma majors would spend around US$1-1.5 billion just for drug trials in India. Big pharma companies like Novo Nordisk, Aventis, Novartis, GlaxoSmithKline, Eisai, Eli Lilly and Pfizer as well as international

Many researchers and pharmaceutical companies are beginning to look at China's and India's massive populations as an asset for clinical trials. Emerging diseases such as Severe Acute Respiratory Syndrome (SARS), and medical conditions that are particularly prevalent in China – such as diabetes and hepatitis – present an opportunity to make rapid advances in clinical research.

Contract Research Organizations (CROs) like Quintiles, Covance, PPD, Parexel, Icon, Omnicare, and Clintec have commenced clinical drug trials across various Indian cities.

CROs which compete with each other to provide clinical trial services for pharmaceutical companies, are mushrooming across India. US companies are acquiring Indian CROs and turning them into hubs for clinical research activities.

India currently participates in about one percent of worldwide biopharmaceutical clinical trials, involving 757 sites, according to an article in *Nature Reviews Drug Discovery*. However, its average relative annual growth rate is nearly 20 percent.

There are hurdles that need to be overcome as well. At the federal level, the central ethics committee at the Indian Council of Medical Research issues guidelines but has limited policing power. There are plans underway to convert the current ethics guidelines into law.

In 2005, the government of India enacted a rule that allows foreign pharmaceutical companies to conduct trials of new drugs in India at the same time that trials of the same phase are being conducted in other countries.

This rule supersedes a directive of India's Drugs and Cosmetics Rules that required a "phase lag" between India and the rest of the world. According to the older rule, if a phase III study had been completed elsewhere, only a phase II study was permitted in India. Even under the newer laws, only those drugs that have already passed phase I safety trials in the country of their origin can be tested on Indians. **PA**

Playing Rules in Competition

Ulf Nehrbass,
CEO,
Institut Pasteur Korea

When it comes to technological development, competition is a major driver of progress. In Asia's more centralistic approach, the general notion is that there is too little competition to start with.

There are however, two sides to the coin: In a well-funded system, competition is a source of motivation and helps in the testing of the validity and robustness of alternative approaches and ideas – it functions as a check point by scrutinizing actual results.

By contrast in a less well-funded system, competition can give rise to problems, with researchers competing for professional, financial and social survival – creating an environment that is toxic to innovation.

The size of the playing field is another important factor: In a country like the US, the duplication of efforts between laboratories and institutions is affordable and desirable, whilst in Asia, it easily amounts to a waste of resources. More importantly, competition requires a mature set of "rules of game," allowing a switch to cooperation where needed, particularly pertaining to national interests.

If it is taken out of context, competition can become a liability. To yield benefits, it has to be administered in careful doses. On the side of decision makers, there should be clear road maps of how cooperation can lead to win-win situations.

By sharing expensive R&D technologies while working on distinct disease areas, Asian pharma can afford the resources to remake itself into an innovative industry. Instead of competing within the region, it should aim to collectively compete in the international arena.

Part four of this series will be featured in the January/February 2010 issue of PharmaAsia and will look at the various business models that are adopted by MNCs.

Animal-Free Solutions for Biopharmaceuticals

Yeast expression systems and proprietary protein engineering technologies provide flexibility in the production of therapeutic proteins with extended circulatory half-life.

Svend Licht,
senior director
Bioprocess Technologies,
Novozymes Biopharma

The demand for safer human therapeutics is growing. In recent years, this increasing need for improved efficiency and safer pharmaceuticals has led to major developments in bioprocessing. Animal-free components offer an ethical and safe solution for the production of ingredients that form the basis of biological products.

The popularity of these ingredients is increasing as regulatory authorities begin to enforce strict quality measures on products to improve safety, particularly with potential contamination risks from pathogens such as viruses in animal-derived ingredients.

The development and application of animal-free solutions for the production of biopharmaceuticals has safety and regulatory advantages and in addition, is economically viable and commercially scalable.

Using Yeast

Saccharomyces cerevisae has a track record in the production of protein therapeutics, such as insulin. It is a species of budding yeast that is commonly used in industry. When researchers investigate organisms to use in their studies, they look for several traits including size, generation time, accessibility, manipulation, genetics, conservation of mechanisms and potential economic benefit.

Saccharomyces cerevisae has developed as a model organism because it scores positively on a number of criteria. As a single cell organism, it is small with a rapid generation time and can be easily cultured. This allows for the swift production and maintenance of multiple specimen lines at low cost.

The yeast can be transformed, allowing for either the addition of new genes or deletion through homologous recombination. Furthermore, the ability to grow it as a haploid simplifies the creation of gene knockouts strains. As a eukaryote, Saccharomyces cerevisae also shares the complex internal cell structure of plants and animals without the high percentage of non-coding Deoxyribonucleic Acid (DNA) that can confound research in higher eukaryotes.

R&D has yielded a series of Saccharomyces cerevisae strains with various desirable traits including genetic stability, high copy number expression plasmids, protease deficient mutants and strains deficient in the enzymes that are involved in o-linked glycolisation.

Protein Expression Systems

Expression systems are used for producing proteins as a result of the expression of recombinant genes encoding the desired polypeptide. Recombinant genes are introduced into expression hosts, using vector systems which allow the gene to be maintained and expressed and which enable the analysis of protein structure and function. The use of recombinant proteins varies widely from functional studies in vivo to large-scale production for structural studies and therapeutics.

Yeast expression systems are useful for the expression and analysis of eukaryotic proteins, providing a flexible, controllable and effective solution for protein expression needs. The

advantages of protein expression in yeast are high yield protein expression, productivity, rapid high cell density growth; stable product strains. Such systems are genetically well characterized and are known to perform many post-translational modifications. Protein expression in yeast is also cost-effective when compared to insect or mammalian cells.

The Saccharomyces cerevisiae-based expression system is optimized for the production of recombinant proteins where glycosylation does not naturally occur or where it can be designed without impacting product efficacy.

Many problems can be overcome that are associated with prokaryotic alternatives. These include the improper disulfide bond assignment, risks of protease degradation and inclusion body formation. The utility of these strains is demonstrated in the success in producing difficult-to-express proteins such as fully functional transferrin.

Albumin Fusion Technology

Albufuse, albumin fusion technology is the molecular fusion of albumin to protein drug candidates for improved half-life and bioavailability. It offers the ability to make completely new therapeutics that were previously out of reach. Using proprietary yeast-based protein expression systems, fusion technology produces albumin that is joined to a therapeutic protein or peptide, defined at the genetic level.

Albumin, which is present in high volumes in the bloodstream, is a choice for drug delivery as it has, no endogenous activity; a naturally long half-life of 20 days; and is an effective carrier for transporting many molecules around the body. The technology has also been shown to increase a protein's half-life from minutes to hours and hours to days.

Animal-free components offer an ethical and safe solution for the production of ingredients that form the basis of biological products.
(Source: Novozymes Biopharma)

The concept is suitable for many peptides and proteins. The heart-shaped albumin molecule has several points, particularly at either of the C- or N- termini, where proteins and peptides can be placed. It is even possible to fuse two different proteins together with albumin in the same recombinant molecule to give two different functions (bivalent) at the same time. This flexibility means that the concept can also be used to make novel products such as bi-functional proteins, in addition to improving existing products.

The technology can be utilized in a variety of protein expression systems. However, a proprietary yeast expression platform has been developed to be particularly effective in producing albufuse molecules. Based on a 2-micron plasmid construct, the system allows the expression of an extensive range of proteins, representing many classes of biotherapeutics. These include protease inhibitors, enzymes, transport proteins, cytokines, anti-angiogenic polypeptides, anti-inflammatory polypeptides and growth hormones.

As a natural alternative to PEGylation, the technology offers a number of advantages including reduced dose rates, reduced side effects, and increased half-life extension of the active molecule. An increased half-life significantly reduces the frequency of administration of the therapeutic protein, which can reduce the overall dosage.

As some biopharmaceuticals have to be administered by a nurse at home or at a clinic, the number of visits can be dramatically reduced, resulting in better compliance and ease of use. Additionally, there is improved stability and shelf life of the proteins.

A significantly reduced dose means that treatment is more cost-effective – an increasingly important consideration due to the growing focus on healthcare costs and accessibility to

medicine. The risk of possible side effects is also decreased as a lower dose means that the toxicity level of the protein within the patient may not be reached.

Instead, the drug dose remains within the therapeutic range, increasing the patient's response to the drug. It has been demonstrated that albufuse-based molecules can lead to more favorable tissue distribution within the body, reducing the risk of localized retention at the site of administration.

Further advantages of using this protein expression system include the ability to generate intact proteins with low cost of goods, due to large scale manufacturing with low purification costs, in a system that is free of animal-derived components. The latter is of rising importance as the regulatory authorities begin to implement strict guidelines around the use of animal-based products and ingredients in pharmaceutical processes and products.

With increasingly stringent safety regulations being placed on biopharmaceutical companies, the demand for products that are free of animal-derived ingredients is increasing. Yeast expression systems and proprietary protein engineering technologies offer the industry tools with which to develop products that only use animal-free ingredients.

By implementing such systems, companies are able to develop a fully defined, animal-free bioprocess. In addition to offering health and safety advantages, yeast expression systems also offer economic viability and commercial scalability. **PA**

The yeast can be transformed, allowing for either the addition of new genes or deletion through homologous recombination. Furthermore, the ability to grow it as a haploid simplifies the creation of gene knockouts strains.

Treatment for Hepatitis C

Protein expression technology can be readily manipulated in direct response to customers' requirements and is able to express an extensive range of proteins, representing different classes of biotherapeutics. Interferon is used to treat people suffering from chronic Hepatitis C viral infections.

However, with a normal half-life of five hours, interferon is soon lost from the body. One way to make it last longer is to use PEGylation, whereby a chemical is bolted on to the interferon. This extends the half-life to 35 hours. However, by fusing interferon to human albumin, the administration is increased to once every two weeks.

Human Genome Sciences has developed Zalbin using albufuse under license and in collaboration with Novartis. In April 2009, positive Phase III results of the treatment in patients with chronic hepatitis C were presented at the annual meeting of the European Association for the Study of the Liver in Copenhagen.

Data from two pivotal Phase III trials showed that the treatment met its primary endpoint of non-inferiority to Pegasys (peginterferon alfa-2a). With half the injections, Zalbin achieved a rate of sustained virologic response that is comparable to Pegasys in these studies, with rates of serious and/or severe adverse events that were also comparable. The treatment has been shown to be biologically active and has the potential to allow a less frequent dosing regime in comparison to a daily dosing regime for the unfused moiety.

Enquiry code: 098E04

Drug Discovery

Electroporation: Transfecting Primary Cells

Using specialized systems, scientists are able to rapidly optimize the conditions for transfecting primary mast cells.

Kelly Kroeger,
senior scientist
Gene Expression Division,
Bio-Rad

The use of primary cells – cells isolated directly from tissues or blood – is rapidly becoming the desired model system for examining physiological processes. Its usefulness is illustrated in the studies of diseases like cancer and diabetes.

Primary cells are a valuable tool for researchers and are often preferred over transformed or immortalized cell lines because they are more representative of cells in vivo. The transfection of these cells provides researchers with a means of examining cellular processes in vitro. This information may lead to the development of more effective therapeutics and diagnostics.

In contrast to immortalized cell lines, primary cells typically undergo minimal cell division and have a finite lifespan in culture, making gene transfer and expression a challenge compared to standard cell lines. Additionally, researchers must use these cells wisely due to the latter's short life spans.

Cell Study

In order to study primary cells, suitable tissue culture conditions to generate and/or maintain the cell of interest must first be developed. Typically, mature primary cells, or immature precursors, are harvested from an animal and are then grown ex vivo as a cell culture.

Hematopoietic stem cells are particularly well suited to growth and differentiation by culturing them in vitro and many different types of blood cells can be generated from bone marrow. One such hematopoietic cell, the mast cell, is particularly amenable to ex vivo differentiation and is comparatively hardy and long-lived.

Mast cells are resident in many types of tissue and contain granules that are rich in histamine and heparin. These cells are understood to be important initiators and regulators in both innate and adaptive immunity, in addition to their traditional roles in allergic and immune responses.

Their role in inflammatory response and immunity is being examined by researchers. It is believed that examining these cells and how they behave will offer greater insight into the body's response to certain diseases like cancer. Because mast cells play a fundamental role in asthma and allergy, these cells represent an excellent primary cell model.

Even after decades of research, getting genetic material inside the cell membrane is still a challenge, specifically when working with frail or scarce mammalian cells. When looking to transfect cells, many options are available. From using carrier molecules or viral vectors to electroporation, researchers may need to test several methods to determine what works best for their cell line.

Electroporation can be used with almost all types of cells to achieve some level of success. In electroporation, the electrical current causes the cell membrane to open and the electrophoretic effect gains entry for the nucleic acids. This is a fast and adaptable method to introduce exogenous nucleic acid into primary cells. While speed and adaptability are important factors, maximizing efficiency and maintaining viability are equally important.

Multiple Applications

There are advantages to electroporation: It is a non-chemical method that does not alter the biological structure or function of the target cells. It is easy to perform (simple push button protocols) and results in high transfection efficiency and cell viability compared to chemical or biological methods. The biggest advantage perhaps is that it is a universal method which can be applied to a range of cell types, including primary and stem cells, in addition to immortal cell lines.

The Gene Pulser is designed for transfecting small interfering RNA (siRNA), plasmid Deoxyribonucleic Acid (DNA) and other molecules into mammalian cells – especially into primary and difficult-to-transfect cells. The system consists of a power module to generate a pulse, a plate chamber, electroporation plates and an optional ShockPod cuvette chamber for choice in delivery vehicle.

Because the system enables not only pre-set protocol but allows for every electroporation parameter and experimental condition to be programmed – from voltage to number of pulses – the ideal conditions for transfecting mast cells are determined. This feature permits the efficient delivery of plasmid DNA to the mast cells. Results demonstrate that using this approach, mast cells can be transfected with efficiency and low cytotoxicity.

Primary mast cell cultures are established from the bone marrow of 8-12 week BALB/c mice. Bone marrow is flushed from the femurs and tibiae and cells are cultured at 1 x 106 cells/ml in Gibco RPMI Media 1640, supplemented with 10 percent fetal calf serum, 1.0 percent L-glutamine, 1.0 percent penicillin/streptomycin, and ß-mercaptoethanol.

Interleukin-3 (IL-3) (10 ng/ml) is added at the initial plating, and every seven days thereafter to promote the differentiation to mast cells. Stem cell factor (20 ng/ml) is added after 14 days, and every seven days thereafter. The medium is changed weekly. After five weeks in culture, mature mast cells are fully differentiated and ready for transfection.

Mast cells are washed once with Phosphate-Buffered Saline (PBS), counted, and suspended at 1 x 107 cells/ml in the electroporation buffer. Plasmid DNA with the Green Fluorescent Protein (GFP) reporter gene (gWIZ GFP mammalian expression vector) is added to the cells at a final concentration of 20 µg/ml.

Subsequently, the cell suspension is transferred into the wells of a 96-well electroporation plate and pulsed using the electroporation system. To determine the optimal electroporation conditions for mast cells, both exponential-decay and square-wave pulses are tested using a variety of settings.

After electroporation, the cells are transferred into tissue culture plates containing pre-warmed Gibco RPMI Media 1640 with 10µg/ml IL-3 and incubated for 24 hours at 37°C. Transfection efficiency and cell viability are determined by flow cytometry analysis, 24 hours post-electroporation. The cells are stained with Propidium Iodide (PI) prior to flow cytometry analysis. Transfection efficiency is expressed as the number of cells expressing GFP relative to the total number of live cells. Cell viability is assessed using PI staining.

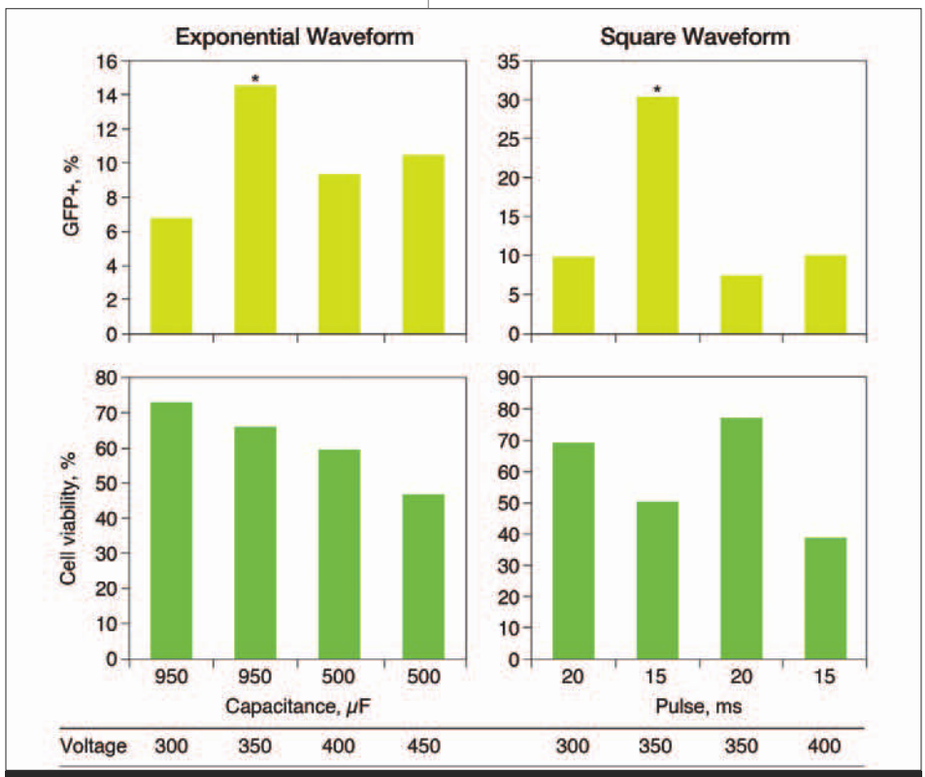


Figure 1. Transfection efficiency and viability of mast cells after electroporation. Cells were electroporated using exponential-decay and square-wave pulses with different parameters. Expression of report GFP (top charts) and cell survival (bottom chart) were monitored 24 hour postelectroporation. The best parameters are indicated by an asterisk. Values are the mean of three replicate experiments. (Source: Bio-Rad)

Drug Discovery

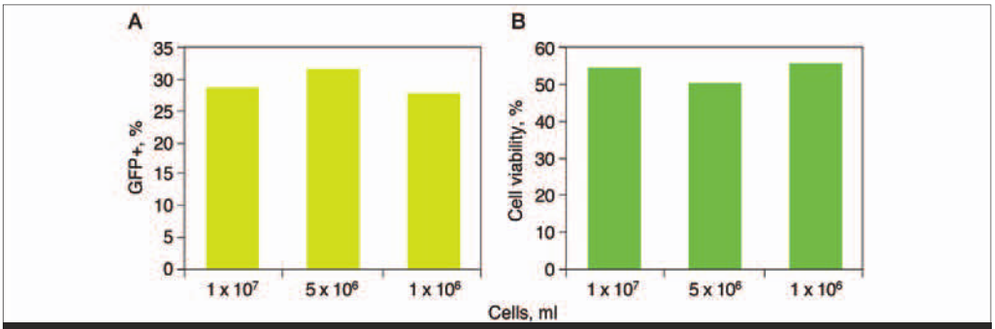


Figure 2. Transfection efficiency (A) and cell viability (B) of electroporated mast cells at three cell densities. All experiments were carried out at 350 V, with a pulse duration of 15 ms. Values are the mean of three replicate experiments. (Source: Bio-Rad)

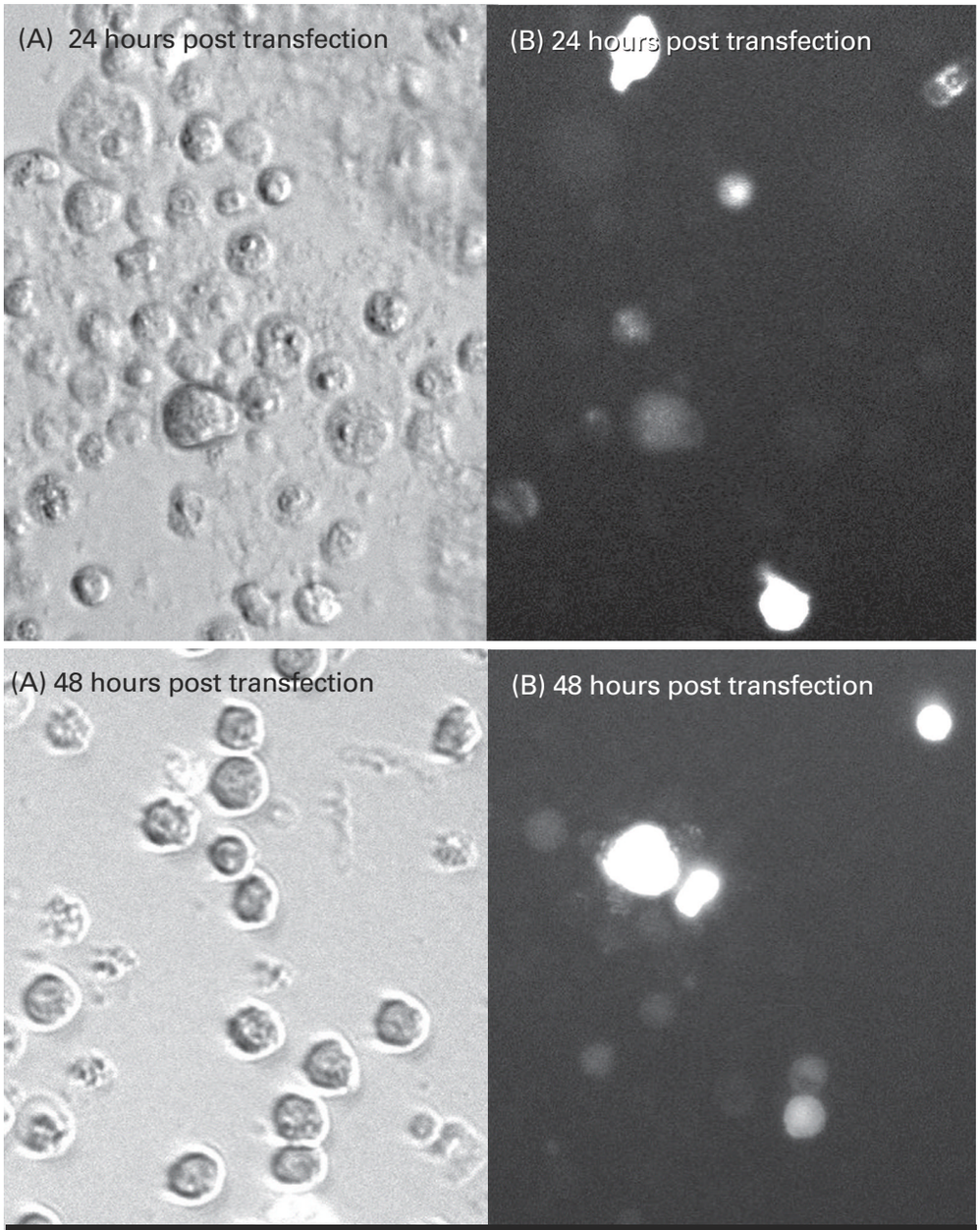


Figure 3. Microscopic observation of mast cells after transfection. A, contrast phase microscopy images of cells; B, corresponding fluorescence microscopy images of cells expressing GFP. (Source: Bio-Rad)

Studying Results

Square-wave pulses are found to be more effective than exponential-decay pulses at delivering plasmid DNA to mast cells while maintaining cell viability (Figure 1). The highest transfection efficiencies are obtained with a square-wave protocol delivering a 15 ms pulse at 350 V; this reproducibly yielded approximately 30 percent transfection rates with approximately 50 percent cell viability. As illustrated in Figure 1, higher cell viabilities can be obtained; however, this is at the cost of reduced transfection efficiency.

The effect of cell density on electroporation efficiency is tested. Cell densities of 1 x 106, 5 x 106, and 1 x 107 cells/ml yielded similar transfection efficiencies and cell viabilities (Figure 2).

Expression of GFP is examined at 24 hours and 48 hours postelectroporation. At both time points, comparable levels of GFP expression relative to living cells are observed, thereby illustrating that these electroporation conditions are suitable for extended time point cell analyses (Figure 3).

Using the electroporation system, scientists have been able to rapidly optimize electroporation conditions for primary mast cells. The results indicate that after a 15 ms pulse at 350 V using a square-wave protocol, roughly one-third of the cells express the reporter gene (GFP). Depending on experimental needs, electroporation conditions can be modified to increase either cell viability or transfection efficiency.

Rapid optimization is particularly valuable when working with primary cells, as conditions may vary substantially for each cell type due to differences in size, granularity, and replicative state. Furthermore, primary cells are often not available in large numbers and are not long-lived. Therefore, the simultaneous examination of numerous electroporation conditions using small numbers of cells reduces the amount of cell culture that is required to obtain sufficient cell numbers for analysis. **PA**

Enquiry code: 098E05

Global Compliance with Analytical Method Validation

Laboratory methods for pharmaceutical analysis need to meet standards in procedure parameters such as accuracy, linearity and precision.

Dr Nealie Newberger,
Crystal[3] Laboratories

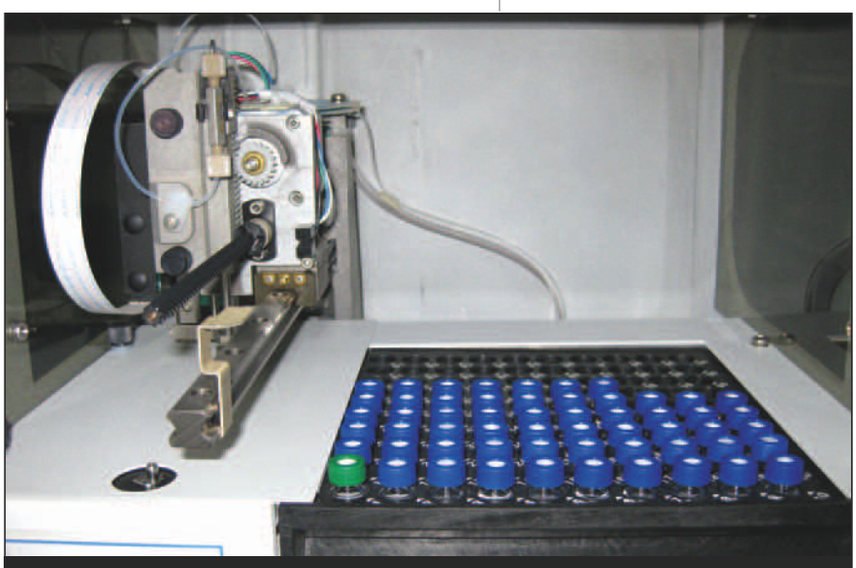
There is a need for the validation of analytical methods in order to determine if the methods that are used in pharmaceutical analysis are suitable for their intended purpose. It is in fact a Good Manufacturing Practice (GMP) requirement. Without a consistent approach to evaluating the analytical methodologies that are utilized in the pharmaceutical realm, a claim cannot be made that the data that is being reported is reliable. Given these suppositions, it is important for the international pharmaceutical industry as a whole to strive for harmonization in analytical method validation requirements.

Adopting Guidelines

A worldwide effort in quality harmonization is already in effect, as demonstrated by the efforts of the International Conferences on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). As seen in the ICH Guideline Q2, Europe, Japan and the US have made a concerted effort to establish a guideline for validation components that are shared by their respective regulatory bodies.

Japan has already adopted these guidelines and has participated in the harmonization process. These necessary components to validation demonstrate if the methods that are utilized for evaluating pharmaceutical products will provide reproducible and reliable data.

In turn, this allows the users to accurately evaluate and interpret the resulting data with confidence. With India and China becoming powerhouses in the pharmaceutical industry, the countries with which they do business will require that they adhere to the same standards. Additionally, many of the smaller Asian countries that are striving to compete in the global market can benefit by spearheading the initiative to comply with the international standards that have been set forth by these various regulatory bodies.



As seen in the ICH Guideline Q2, Europe, Japan and the US have made a concerted effort to establish a guideline for validation components that are shared by their respective regulatory bodies. (Source: Crystal[3] Laboratories)

It is generally agreed upon that two phases must be addressed in this process: the method development phase in which the assay is defined, and the method validation phase. Sometimes, these two phases are grouped together but the requirements remain the same. The method development stage should begin with identifying the kind of assay that is necessary for product analysis. This involves developing a stability indicating assay, or an assay that can detect changes with time in the pertinent properties of the drug substance or drug product.

The assay should also be able to accurately measure the active ingredients without interference from degradation products and process impurities, as defined by Saji Thomas, associate director at Par Pharmaceuticals. Once this is believed have to been accomplished, the assay can be evaluated for robustness. Robustness is an important criterion for stability indicating assays. It is typically evaluated by varying certain parameters of the test method

such as sample pH, flow rates, detection wavelengths and the organic composition of the mobile phase for High Performance Liquid Chromatography (HPLC) assays.

Evaluating Reliability

By varying these parameters and evaluating the integrity of the resulting data, one can determine if the method is indeed robust or rugged. This indicates how reliable the method will be under everyday usage according to the ICH Q2 guideline.

Proceeding to the method validation phase, the method can then be further evaluated on multiple levels and the true nature of the method ascertained. The data that is generated for a typical analytical method validation for drug substances should address the following parameters: accuracy, linearity and precision: repeatability and intermediate precision, specificity, and range.

The stability of the solutions and materials that are needed should also be addressed. According to Nowatzke and Woolf, solution stability may be addressed at a separate time – perhaps during the method development phase would be most appropriate. Without solution stability determination, it is difficult, if not impossible to evaluate a method for the above mentioned parameters. Additional considerations include evaluating the Limit of Detection and the Limit of Quantitation.

Both the ICH Q2 Guideline, the Japanese Pharmacopeia (JP) general chapter [118] and the general validation monograph <1225> listed in the current US Pharmacopeia (USP) provide comprehensive outlines or charts. These suggest appropriate testing criteria for not only the assay of a drug substance, but also for impurity testing, content uniformity testing, dissolution testing and identification testing.

According to the USP, different testing procedures require different testing schemes. Evaluating the requirements for the target project is a critical step before proceeding with the lengthy validation process. Missing such a step could cause costly set-backs in product evaluation. Chart 1 outlines the data requirements that are found in the current USP monograph.

Analytical Performance Characteristics	Category I	Category II		Category III	Category IV
		Quantitative	Limit Test		
Accuracy	Yes	Yes	*	*	No
Precision	Yes	Yes	No	Yes	No
Specificity	Yes	Yes	Yes	*	Yes
Detection Limit	No	No	Yes	*	No
Quantitation Limit	No	Yes	No	*	No
Linearity	Yes	Yes	No	*	No
Range	Yes	Yes	*	*	No

*May be required depending on the nature of the specific test

Chart 1: Data Elements Required for Validation (Source: Crystal[3] Laboratories)

• **Category I** is recognized as analytical procedures for the quantitation of major components of bulk drug substances or active ingredients (including preservatives) in finished pharmaceutical products.

• **Category II** is recognized as analytical procedures for the determination of impurities in bulk drug substances or degradation compounds in finished pharmaceutical products. These procedures include quantitative assays and limits tests.

• **Category III** is recognized as analytical procedures for the determination of performance characteristics (eg, dissolution testing or drug release testing).

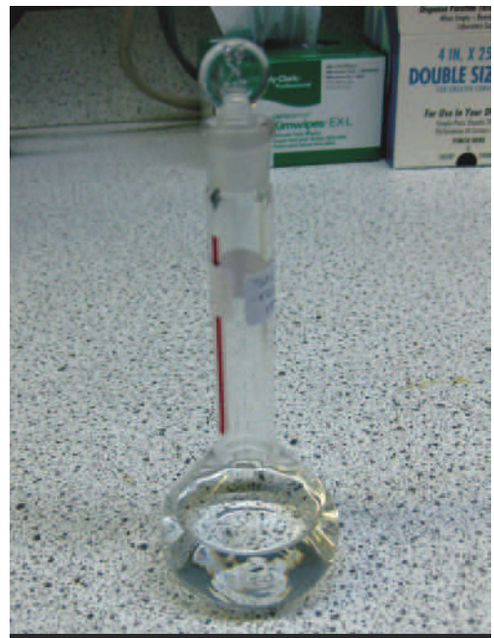
• **Category IV** is recognized as identification tests.

Assuming that a Category I method validation will be required. Once the category is defined, the key components to the validation are easily identified via Chart 1 and a validation plan can be organized. It is important to understand the function of each of the required tests. For example, the following are definitions of the key components of method validation as listed in the ICH Q2 Guideline, which are easily adaptable in any analytical laboratory:

• The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted, either as a conventional true value or an accepted reference value, and the value found.

This can be determined by preparing three replicate preparations of spiked placebo at 80 percent, 100 percent and 120 percent of the nominal concentration of the product. Typically, a mean percentage recovery at each concentration should be 100 +2 percent.

• The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements that are obtained from the multiple sampling of the same homogeneous sample under prescribed conditions. Precision may be considered at three levels: repeatability (intra-assay), intermediate precision (different days, different analysts, etc) and reproducibility (between laboratories).



The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted, either as a conventional true value or an accepted reference value, and the value found. (Source: Crystal[3] Laboratories)

Regulatory & Compliance

Intermediate precision can be evaluated by having a second analyst repeat the accuracy test on a different day and with a different HPLC column and instrument. (Source: Crystal[3] Laboratories)

System suitability should also be evaluated by making replicate injections (6) of a 100 percent standard solution. The percent Relative Standard Deviation (%RSD) of those should be <2.0 percent . Intermediate precision can be evaluated by having a second analyst repeat the accuracy test on a different day and with a different HPLC column and instrument. This can also be accomplished by repeating the test at a different laboratory. The %RSD of both analysts' data combined should be < 2.0 percent.

• The linearity of an analytical procedure is its ability within a specified range to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.

This can be determined by evaluating serial dilutions of a stock standard covering 80 percent to 120 percent of the nominal sample concentration prepared in duplicate. Five to eight concentrations are typically chosen.

• The range of an analytical procedure is the interval between the upper and lower concentration amounts of an analyte in the sample for which the analytical procedure has a suitable level of precision, accuracy and linearity.

ICH recommends a range of 80 percent to 120 percent be evaluated for the assay of a drug substance.

• The detection limit of an analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated.

A solution that generates an active peak with a signal to noise ratio of 3:1 is typical.

• The quantitation limit of an analytical procedure is the lowest amount of the analyte in a sample which can be quantitatively determined with suitable precision and accuracy.

A solution that generates an active peak with a signal to noise ratio of 10:1 is typical.

• The specificity of an analytical procedure is its ability to assess unequivocally, the analyte in the presence of compounds that may be expected to be present, such as impurities and degradation products and matrix components.

Specificity can be assessed by degrading the sample preparations via acid, base, peroxide, heat and light stressors. The degraded products can then be analyzed and compared with a freshly prepared sample.

Having a good understanding of typical method validation can make a large project seem less overwhelming and more approachable. While the Western world and Japan have made method validation a commonplace amongst analytical laboratories, much of Asia has yet to do so. Utilizing supporting documentation on method validation such as the appropriate monograph or chapters in the USP and JP, or the ICH Q2 Guideline, will provide the initiating laboratory with the specific details that are necessary to begin method validations.

Conference reports such as Bioanalytical Method Validation – A Revisit with a Decade of Progress by Shah, VP, may also prove useful. In any instance, there is a global need for harmonizing method validation requirements in the pharmaceutical industry. Ultimately, implementing analytical method validation practices as a regular set of analyses that are performed in the laboratory on new and existing products, can provide potential customers with confidence in the products that they purchase. **PA**

Enquiry code: 098E06

API China (Beijing)

The winter edition of the show in 2009 is witnessing growing cooperation between Indian and Chinese pharma companies.

API China is a show that is "rotated" between different tier one or two cities. Its location is chosen, based on the cluster of relevant industries that are in the host city.

In the Beijing 2009 edition, most overseas visitors arrived from India, South East Asia, Japan, Korea and Hong Kong. From Europe, visitors were mainly from Germany Italy and France.

The event featured more than 1,200 exhibitors over an area of 55,000 sq meters and was attended by 30,000 visitors. There were 46 conference and seminar sessions.

The Indian Buyer Port (IBP) has seen an increase in the number of booths to 20, up from 11 in the previous show in Xi'an.

Daniel Chan, director, Reed Sinopharm Exhibitions believes that the next show that will be held in Harbin in 2010 will host approximately 25 IBP participating companies. **PA**

Exhibitors

Capacity Expansion

Wan Gui Sheng,
GM and president, Guangzhou Zhongnan Pharmaceutical

Our company manufactures Active Pharmaceutical Ingredients (API), and natural plant extract products such as Star Anise Oil, Camellia Oil and Eugenol. We are certified by the State Food and Drug Administration (SFDA).

About 70 percent of our revenue comes from the domestic market. Around 50 percent of our products are exported to Taiwan and Italy. The other half of our exports is taken up by Hong Kong. Next year, we are aiming to export to additional markets in the US, Europe and Japan. We also have plans to attend overseas exhibitions to meet more buyers.

Our upcoming factory in the Jiangxi province will be ready in July 2010, and will allow us to introduce new products in the market. The factory will span a total area of 91,000 sq meters, with 82,000 sq meters being taken up by the production line. Our company is targeting to obtain certification by the US FDA in next 1-2 years.

Competition in the export market is intense. As our company focuses on quality, the cost of our products tend to be higher than those of our competitors. This puts us at a disadvantage in terms of product pricing. The economic crisis however, served as a blessing for us. Many of our competitors were not able to survive the changing market climate, while at the same time, our focus on quality has made us more attractive to buyers. PA

Hu Jian,
president, DSM China

Environmentally Friendly

DSM is a manufacturer of API, mainly for anti-infectives. We started our business in China about 10 years ago. We supply most of our APIs to the local market. We also export intermediates to our sister companies in Europe and India. We currently develop our technology in Europe and then introduce it into China. For example, we are launching our "Green Enzymatic Technology" which is to be used for the production of Cefalexin at our Zibo site.

The main advantage of this technology is that it replaces the chemical process (which consumes large amounts of solvents). It can reduce the amount of solvents that are released as waste each year by over 1000 metric tons, and also helps to cut costs. In addition the purity of the product is increased – impurities are reduced from one percent to less than 0.5 percent.

In the next five years, our plan is to double or triple our annual turnover in China. PA

Cost & Quality

Zhang Yong,
president, Changzhou Chemical Research

Our organization started off as an academic research institute in 1976, involved in the research of chemicals. We are now a Contract Research Organization (CRO)/ Contract Manufacturing Organization (CMO), performing activities ranging from R&D to manufacturing as well as sales.

We supply intermediates to patented drug manufacturers such as Boehringer Ingelheim, Novartis and GSK. We may also be supplying to Roche next year. We also sell our products to generic drug manufacturers in India like Hetero Drugs, Shasun Chemicals, Divis Laboratories and Hikal.

Our company has two factories – one in Changzhou and the other in Dafeng. We also have a laboratory in Changzhou and another in Shanghai.

Our marketing strategy is based mainly on overseas markets. More than 50 percent of our revenue comes from the US. The rest comes from Europe (20 percent), Japan (20 percent) and India (10 percent).

In future, we would like to expand further into supplying intermediates for the generics market, especially in India. We expect strong competition in this country, which means that our prices need to be competitive. We are also looking to move into Brazil.

With the patent drugs market, the focus is on quality and technology. For generic drugs, price also becomes an important factor. Our challenge is to find a balance in both these areas of our business.

As patent drugs will eventually "become" generics, our aim is to enter the patent drugs market early and achieve success in this arena. This will provide us with the experience and cost advantage in the generics market later on. PA

Sunny Bai,
sales director, Jiangsu Zodiac Marine Biotechnology

Export Focus

We are a Hong Kong company that manufactures seaweed- and vegetable-based capsules. These products are patented and we produce 30-50 million capsules every month.

In 2009, we started our export business. Our three main target markets are the US, South East Asia and the Middle East. We are currently exporting to countries like Thailand, Singapore, Pakistan, Malaysia and Indonesia. We will be opening an office in the Middle East next year.

From a global perspective, vegetable-based capsules are seeing growing demand. Due to its relatively higher price and a lack of knowledge of this product, domestic demand is limited. Most of our product is destined for overseas markets.

We price our products lower than our competitors. Eg, one of our competitors offers their product at RMB 700 (US$102) per 10,000 capsules, while ours is priced at RMB 400 (US$58) for 10,000 capsules.

The company's annual turnover is RMB 1 billion (US$146 million). If the US market manages to shake off the recession, we expect to increase turnover by 20 percent next year.

Our company has SFDA certification based on Good Manufacturing Practice (GMP) guidelines. We are also ISO 2000 and Halal certified.

Our five year plan is to achieve RMB 4 billion (US$585 billion) in sales revenue by 2014. We also have plans to introduce the "liquid capsule" into our product line at a selling price of RMB 500 (US$73) per 10,000 capsules. **PA**

Lin Xianda,
GM, Zgong Shan Changjian Medicine Packing Material

Controlling Market Share

Our company produces non-PVC films that are used in the manufacture of flexible bags for intravenous drug systems. We are the only company in China that has researched and patented this technology. There are seven other companies in China that supply this product using imported technology.

We are the only company that has been awarded the "State Major New Product" certificate for our non-PVC films. In addition, our company meets GMP standards and holds the "Medicine Packing Material & Container Registered Certificate." We offer various bags that are made from different raw materials, which are customized to contain different types of drugs.

Our films can also be used to produce bags that have multiple separate compartments; each compartment contains a different drug. When the bag is compressed, the drugs are mixed to form a single solution.

Singapore, Japan and Denmark currently purchase our products. We currently hold 10-15 percent of the Chinese market.

The US was the first country to introduce this product into China. They used to hold 85 percent of the market share. Japan has launched an inspection system to test the product. US products are unable to meet this standard and now have a 30 percent share of the market. Germany has about 40 percent while Chinese products account for 30 percent.

I believe that China's market share will increase in the next few years. One of the reasons for this is that Chinese companies can offer quality products in this market segment at a lower price.

US-made five-layer films have a selling price of about RMB 15.5 per sq meter. China-made five-layer films are priced at RMB 12 per sq meter.

German-made three-layer films are available at RMB 11.5 per sq meter, compared to China-made versions, which are sold at RMB 11 per sq meter. **PA**

Indian Buyer Port

Business Development

TK Mohan, president; Innovative Health Care (India)

KM Sakthivel, CEO

India is sourcing for large quantities of raw materials and intermediates from China. Some trading agencies have sent their representatives to this show. These agencies typically act on behalf of a number of small and mid-sized Indian pharmaceutical companies to source for products.

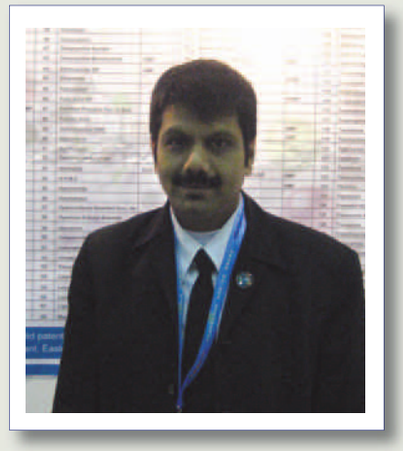
Some of these products can be 10-30 percent cheaper in China compared to India. This event also allows us to get to know about new products in the market. It also serves as a starting point for us to make contact with potential suppliers and then visit them later. The availability of interpreters helps us to overcome the differences in language. PA

Lalit Kumar Jain, director, Pharmchem

Cost Effectiveness

This is our first time at API China. I feel that this show is more focused on APIs, compared to other shows. We have been able to meet the smaller supplier companies. The show is an avenue for us to deal directly with suppliers instead of traders, which allows us to reduce our costs by about 10-15 percent.

Interpreters have been assigned to us at no extra cost (compared to RMB 400 in some of the other shows). Their command of the English language is also relatively stronger. PA



Dhiren Shah, director, Eastern Chemicals

Long-Term Relationships

We are a family-run business and have been importing pharmaceuticals from China for the last 42 years. We currently have about 90 suppliers from China and we are using this event to meet up with some of them here. We are also looking for suppliers of new products.

We have about 9-10 new products on our list and our aim is to shortlist 8-10 suppliers for each product.

IBP has been well promoted prior to the event, which I believe has helped to attract a number of potential suppliers who visited our booth. PA

Seeking Potential

I like the idea of allowing buyers to have booths. This makes it easier for us to meet Chinese suppliers. We are interested in large suppliers as well as the small and medium sized ones that have growth potential.

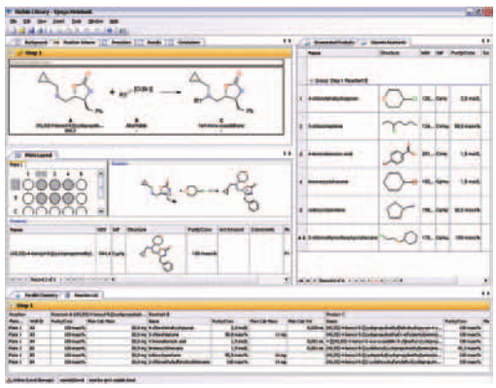
We made suggestions at the show last year, which have been implemented by the organizers. Eg, having the Sino-India Partnership Program (SIPP) pavilion in a U-shaped layout instead of a straight line – which has helped to increase our visibility. PA

Enquiry code: 098E07

Dipak Mehta, MD, Chephis Corporation

Product Focus
Software

Symyx Supports R&D Across Scientific Disciplines



Symyx Technologies has released Symyx Notebook 6.3, a version upgrade. Previous versions focused on biology, analytical and synthetic chemistry. Version 6.3 adds parallel chemistry support for synthetic and medicinal chemistry.

This version enhances the general utility of Symyx Notebook and improves scientists' ability to collaborate across the enterprise. It enables researchers to manage experimental workflows, capture intellectual property and share knowledge.

The software improves support for synthetic chemists, analytical chemists and biologists in regulated and non-regulated environments by offering capabilities including support for parallel synthesis, library enumeration, searching of enumerated reactions and solid phase organic synthesis.

Key features include support for in-depth chemical representation combined with configurable library enumeration capabilities; expansion of exact and substructure searching, which permits the retrieval of fractional salts and hydrates; enabling of solid phase organic synthesis through the implementation of loading units and calculations; "QuickData" capabilities that speed information capture with enhanced procedure editing and standard phrase lists for procedural text.

Symyx, www.symyx.com

Enquiry code: 098P01

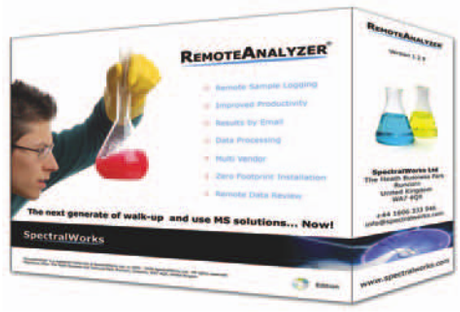
See more products & equipment at www.PharmaAsia.com.

SpectralWorks offers Efficiency in Mass Spectrometry

The RemoteAnalyzer from SpectralWorks extends the "walk-up and use" approach to Mass Spectrometry (MS). In many cases the high throughput approach means that many users are not specifically trained mass spectrometrists.

Open access software allows mass spectrometry to be fully utilized as a research tool in wider application fields that have their own specialists, as they no longer need to have the day-to-day hands on capabilities to run MS samples.

RemoteAnalyzer is an open access solution with support for multiple vendors' hardware. The server based, easy-to-use system allows sample acquisition regardless of which vendors' instruments are being used.



A consistent user interface allows the analyst to review the data processing results. The solution is deployed in environments of routine sample analyses for 15-20,000 samples per year with the added benefit of fast sample turnaround to increase productivity, scope and quality of research.

Spectralworks, www.spectralworks.com

Enquiry code: 098P02

Novatek: Process Control

Novatek International provides pharmaceutical, biopharmaceutical, biotech and chemical companies with regulatory compliant (process-based software) solutions. The company's suite of laboratory and quality management solutions offer quality management, quality assurance and the use of risk management tools which lead to quality control.

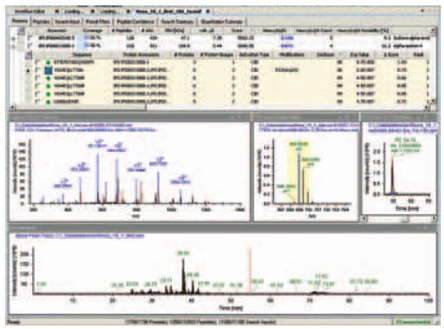
The software solutions help to optimize current manufacturing processes, lower costs, increase productivity, enhance compliance, improve quality measurement, meet Turn Around Times (TAT) and holding times, and prevent missed sampling events.

The software solutions allow companies to manage, control and report their data in compliance with 21 CFR Part 11 and other international guidelines.

Novatek, www.ntint.com

Enquiry code: 098P03

Increasing Productivity in Proteomics



The updated Thermo Scientific Proteome Discoverer 1.1 software is a complement to mass spectrometers, providing a platform for the analysis of qualitative and quantitative proteomics data.

The software includes enhanced capabilities for relative quantitation via isobaric labeling such as Tandem Mass Tags (TMT), batch searching, automated processing via a daemon, improved handling of large datasets, support for Multidimensional Protein Identification Technology (MudPIT) experiments and the ability to merge data from multiple experiments.

Discovery data from the software can be imported directly into the company's Pinpoint software to accelerate the development of targeted quantitative experiments.

Thermo Fisher Scientific, www.thermofisher.com

Enquiry code: 098P04

Calendar of Events

Jan 21-22, 2010
Pharmacovigilance 2010
Mumbai, India.
www.virtueinsight.com/site/Pharma_Details.aspx?SC_ID=3

Jan 25-27, 2010
World Pharma Outlook Asia 2010
Singapore
www.terrapinn.com/2010/pharmaoutlook/

Feb 1-4, 2010
2nd International Conference on Drug Discovery & Therapy
Dubai, UAE
www.icddt.com

Mar 4-5, 2010
Asia Pharma R&D Leaders 2010 Summit
Pudong-Shanghai, China
www.aprdl.com/

Mar 5-7, 2010
IndiaMART India International Pharma Show
Hyderabad, India
www.iipshow.com/

Mar 16-19, 2010
Pharma & Biotech Supply Chain Asia 2010
Singapore
www.terrapinn.com/2010/pharmascm/

Mar 16-19, 2010
Drug Discovery Technology World Asia
Singapore
www.terrapinn.com/2010/drugdiscovery/

Mar 16-19, 2010
Biologic Manufacturing World Asia
Singapore
www.terrapinn.com/2010/biologicasia/

Apr 21-23, 2010
P-Mec Japan 2010
Tokyo, Japan
www.pmec-japan.com/eng

Apr 21-23, 2010
ICSE Japan 2010
Tokyo, Japan
www.icsejapan.com/eng/index.html

Apr 21-23, 2010
Cphl Japan 2010
Tokyo, Japan
http://www.cphijapan.com/eng

Apr 23, 2010
Frost & Sullivan Asia Pacific Healthcare Awards
Singapore

May 31 - Jun 2, 2010
ISPE Conference
Singapore
www.interphexasia.com/

Jun 1-2, 2010
Interphex Asia
Singapore
www.interphexasia.com/

June 2-4, 2010
Cphl China
Pudong-Shanghai, China
www.cphi-china.com

June 2-4, 2010
Bangalore Bio
Bengaluru, India
www.bangalorebio.in/2010

June 16-19, 2010
Propak Asia 2010
Bangkok, Thailand
www.propakasia.com

For more listings, visit www.PharmaAsia.com/events.asp
If you wish to get your event listed, please send the details to laura.low@rbi-asia.com

AD INDEX

Our focus: your compliance.

Our innovative technologies combined with our understanding of industry requirements and our commitment to work with you ensure your compliance. You can rely on us to thoroughly assess the risks you face and help you optimize your processes and quality system performance. Endress+Hauser: your partner in creating value. www.endress.com/life_sciences

Endress+Hauser
Instruments International AG
Kägenstrasse 2
4153 Reinach/BL1
Switzerland

Phone +41 61 715 81 00
Fax +41 61 715 25 00
info@ii.endress.com
www.endress.com

Endress+Hauser
People for Process Automation

The only thing that has cut more paperwork than our software.

Werum's PAS-X, the market-leading MES with shear power.
Smart bio-pharma companies need to work leaner, smarter, and with a greater emphasis on compliance and quality control than ever before. That's why 14 of the world's top 20 pharmaceutical and biotech companies use Werum's product suite PAS-X to run their manufacturing business. They know that PAS-X can drastically reduce a company's paperwork; as importantly, it can easily fit into the processing environment to help streamline manufacturing, improve product quality, and assure compliance. Find out how Werum can easily become your company's choice for trimming waste down to size.

www.pas-x.com

Headquarters
Lueneburg, Germany

US Headquarters
Parsippany, NJ

Asia-Pacific Headquarters
Singapore

Tokyo Office
Tokyo, Japan

werum
SOFTWARE & SYSTEMS