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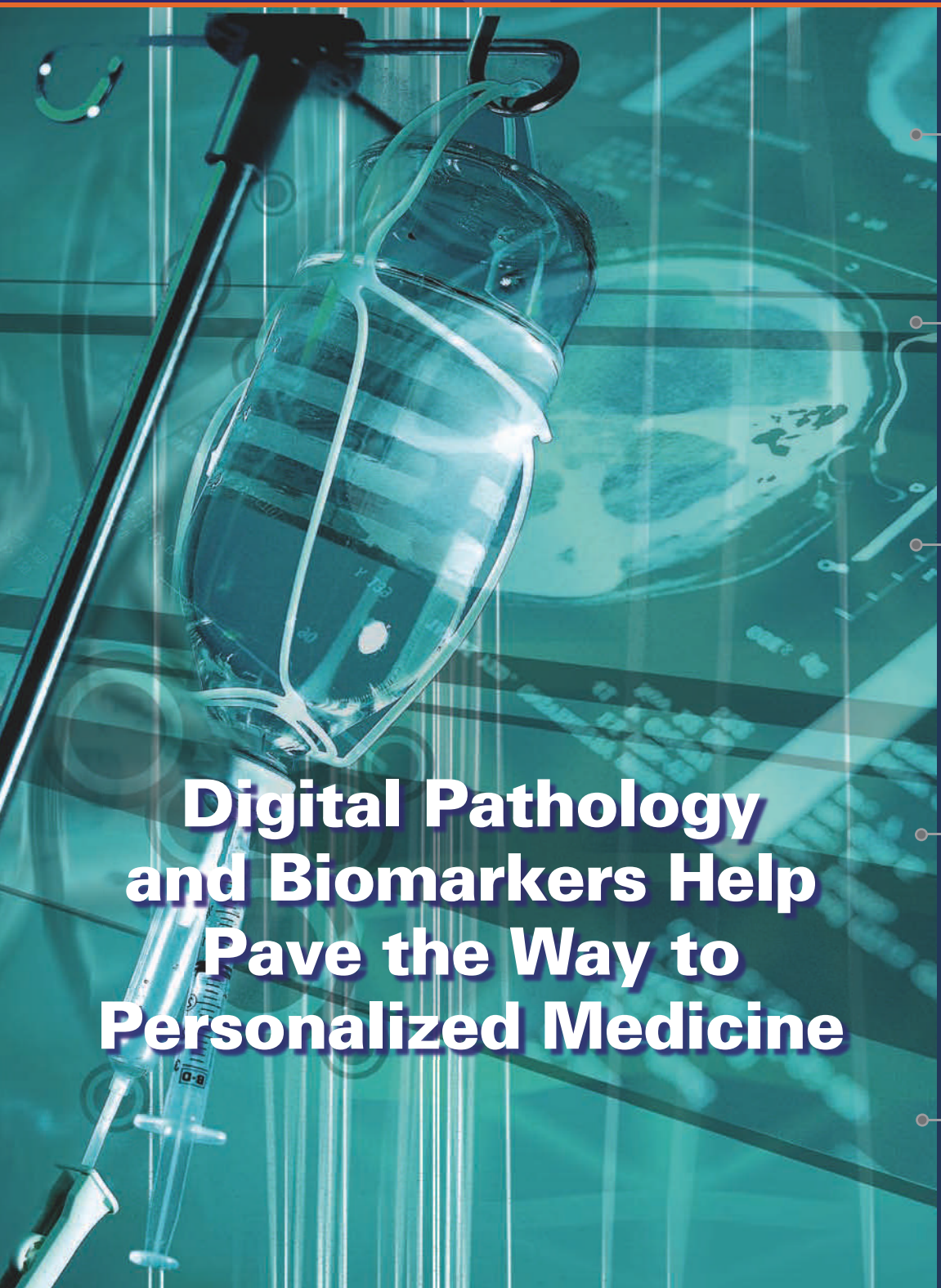

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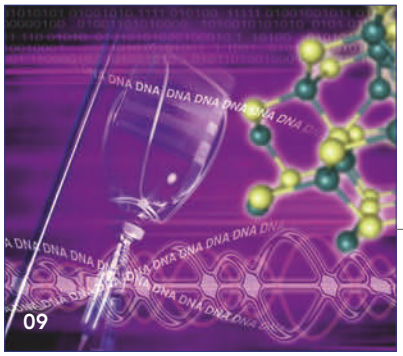

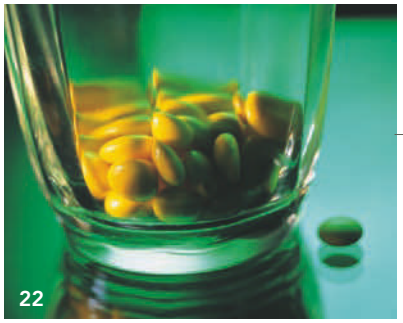

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Editor's Note

Michael Tham
Editor

A Fresh Start

As businesses crank up their engines at the start of a new year, the economic landscape appears to carry a hope of recovery and rejuvenation – albeit a cautious one. Many have emerged from the tumult of last year's meltdown, wiser and better prepared for the challenges ahead.

In this issue of *PharmaAsia*, we feature a special Industry Outlook segment where industry leaders share their views on what to expect in 2010.

Perhaps symbolic of a new beginning, following the recent merger between Integra Biosciences and Viaflo Corporation, the companies have adopted the corporate brand – Integra, starting January 1.

China-based Hard to Treat Diseases (HTDS) has recently passed its "First Drug Evaluation" by the State Food and Drug Administration (SFDA), for the former's MMR (Measles, Mumps and Rubella) combined vaccine. The company estimates the market size in China to be 60 million doses per year.

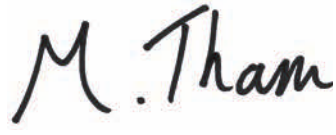
As a testament to greater cooperation in the pharma playing field, Qiagen Asia Pacific and WuXi AppTec have commenced a partnership in Shanghai to provide an integrated single solution. The partnership is for molecular biomarker development, validation and personalized healthcare targets for the companies' respective client bases.

India-based Ranbaxy – a heavyweight in the generics market – has kicked off the year with a promising start as well. The company has launched a New Chemical Entity (NCE), Lulifin (Luliconazole), in the Indian Dermatology market. This milestone follows an in-licensing agreement with Japan's Summit Pharmaceuticals International, giving the former exclusive marketing rights in India.

At the international level, GlobalData has forecasted the Acute Ischemic Stroke (AIS) market to expand at a Compound Annual Growth Rate (CAGR) of 3.4 percent. According to the report, this historically static market offers potential for a pharmaceutical manufacturer whose drug can meet the needs of the market – if it can overcome existing product weaknesses and major adverse effects such as Intracranial Hemorrhage (ICH).

This is perhaps reflective of the competitive world that we live in, where opportunities for growth can be capitalized on – after one manages to rise above current circumstances and prevail over obstacles that stand in the way.

As things return to near normality, the survivors of 2009 can look forward to a fruitful year, equipped with lessons from the past – and a tenacity for success. **PA**



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Pfizer and Strides Arcolab to Collaborate on Generic Products

Pfizer and Strides Arcolab have announced a collaboration, wherein Pfizer will commercialize off-patent sterile injectable and oral products in the US through its Established Products Business Unit.

These finished dosage form products will be licensed and supplied by Strides and Onco Laboratories and Onco Therapies, two joint ventures between Strides and Aspen, South Africa, in which each has a 50 percent ownership interest.

The first of the products that are commercialized under this collaboration are expected to be launched in 2010. **PA**

Artes and Rhein Minapharm Continue Joint Product Development

Artes Biotechnology and Rhein Minapharm Biogenetics have jointly announced the production of a target of a therapeutic protein. The former applied its Hansenula technology platform and know-how to the generation of a therapeutic protein that was chosen by the latter – that is typically produced in *E coli*.

Rhein Minapharms´s target is now produced from the Hansenula polymorpha platform at higher yields and at reduced costs compared to alternative bacterial or yeast systems.

Under the terms of agreement, the former has handed over the production cell lines and has received another milestone payment.

Both companies have extended their collaboration, aiming at additional targets for Minapharm´s portfolio. Artes will be responsible for the generation of new production cell lines and will share the process research and development responsibility with the latter. **PA**

PPD Selected as Exclusive Partner by DiabetesAmerica

PPD has entered into an exclusive alliance with DiabetesAmerica, a provider of diabetes care services based in Houston, Texas. Under the agreement, the former will provide clinical research training and support to more than 20 clinical trial investigators who will conduct type 1 and type 2 diabetes clinical trials from the latter's 17 centers across Texas and Arizona.

In return, the latter will work exclusively with the former to provide clinical research services for endocrine and metabolic disease development programs over a minimum of three years. The agreement expands PPD's ability to recruit for diabetes-related clinical trials through the use of DiabetesAmerica's 16,000-plus patient database. **PA**

OncoMed Pharmaceuticals and Fluidigm Corporation Announce Collaboration

OncoMed Pharmaceuticals and Fluidigm Corporation have announced an initiative to apply the latter's microfluidic tools to the analysis of tumor cell heterogeneity, including cancer stem cells. The collaboration will combine the latter's microfluidic platforms with the former's cancer stem cell sorting technology to generate tools for analyzing, quantifying and developing treatments that are directed at a tumorigenic cell population.

In the initial application, OncoMed will apply Fluidigm's BioMark System and Dynamic Array Integrated Fluidic Circuits (IFCs) to perform the gene expression analysis of solid tumors at the whole tumor and single-cell level. This phase will track changes in cancer stem cells that are found in human tumors, following treatment with the former's pipeline of therapeutic monoclonal antibodies.

The companies will apply this same technology to analyze tumor heterogeneity and cancer stem cell frequency across the former's proprietary human tumor bank which includes approximately one hundred human tumor biopsies that have been engrafted and minimally passaged in immunocompromised mice. **PA**

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Vaccines: Big Players Push into Asia

Vaccines have become an important revenue driver for the pharmaceutical industry. Facing the patent cliff of their existing portfolio of drugs, and encouraged by the emergence of blockbuster vaccines, almost all major pharmaceutical companies have entered the fray over the past 10 years, leading to a consolidation of the industry which is now dominated by just five big players.

Increasingly, these companies realize the commercial opportunity for vaccine makers in emerging and developing countries. Large birth cohorts that dwarf those that have been seen in the developed western world, higher disease burden and rising public and private spending on health make Asia's markets particularly attractive for the vaccine industry, according to Datamonitor.

Looking to Asia

The developed world has been the initial focus of vaccine makers due to established healthcare infrastructure and high price levels, but increasingly competitive and saturated markets have led vaccine developers to look elsewhere, such as Asia. "Here, governments are increasing their efforts to improve vaccination rates and to assure supply, while the growing middle classes are creating a significant private sector opportunity in many countries," says Datamonitor senior healthcare analyst Hedwig Kresse.

It was found that a key argument for vaccine manufacturers to target Asia's emerging markets is demography. China and India, the world's two most populous countries, offer a vast market opportunity for vaccine makers due to their sheer population size, reflected in their large birth cohorts.

These are particularly relevant for vaccine makers as they guarantee a stable demand for infant vaccines. India's birth cohort is almost six times as large as that of the US, and despite China's one-child-policy, there are still more than 18 million babies born every year. In combination with the large need even for basic vaccines, this translates into a promising commercial opportunity for vaccine makers, and a challenge for governments as the main payers.

As immunizations remain one of the key measures to reduce disease burden in countries with high prevalence rates for many infectious diseases, vaccine makers can hope for an increasing readiness of governments to introduce their vaccines and promote or even mandate their use.

Vaccines also have a commercial perspective in the emerging Asian private sector markets, with many people willing to pay out-of-pocket to protect their children from disease. The increasing wealth in India, China, Taiwan and South Korea is leading to a rapid growth of healthcare spending there. Benefiting from the economic upturn over the last decade, these countries are investing more money into healthcare.

While Taiwan and South Korea in particular have significantly increased their spending power and are closing in on the five major European countries (5EU: France, Germany, Italy, Spain and the UK), in terms of gross domestic product per capita, their total healthcare expenditure is still only approaching around 50 percent of the level seen in the 5EU. At the same time, the increasing income level has resulted in a sharp upturn in private sector healthcare spending in the four key Asian emerging markets. It accounts for more than 80 percent of all healthcare expenditure in India, with China, Taiwan and South Korea averaging around 50 percent.

Meeting Needs

Asian markets have varied and differentiated needs that require product offerings that are targeted to the respective country. In terms of disease coverage, there are several different opportunities for vaccine suppliers, ranging from the more basic roll-out of the World Health Organization's Expanded Program on Immunization (EPI) vaccines to higher priced products such as recombinant hepatitis B- and conjugate Haemophilus influenzae type B vaccines.

In the private payer market, there is increasing demand for the provision of new, high-priced vaccines such as pneumococcal conjugate vaccines (such as Prevnar and Synflorix), human papillomavirus vaccine (such as Gardasil and Cervarix), rotavirus (such as Rotateq and Rotarix) and varicella (such as Varivax and Varilrix) vaccines.

There are some diseases that are endemic in Asia whose burden could be reduced by development and/or the introduction of routine immunizations. These include Japanese encephalitis, dengue fever, hand foot and mouth disease, and chikungunya. Using differential pricing, vaccines protecting from these diseases could be offered at a premium to travellers in the West.

In addition to the different needs in terms of epidemiology, regional vaccination coverage rates and recommendations vary widely across Asia's main economies, as do the regulatory environments. Since these variations are significant and are not always transparent or publicized, local knowledge is key for optimum business success.

Key players such as GlaxoSmithKline, Sanofi-Pasteur and Novartis have all acquired smaller enterprises or entered into partnerships in key Asian markets. On-the-ground presence not only lowers the barriers when negotiating with local regulatory agencies and payers, but "can be crucially important for manufacturing vaccines in quantities and at price levels that meet the demands of the host country," adds Kresse.

GlaxoSmithKline's activities in China illustrate these efforts: originally established in 2001, the company expanded its local presence by entering into agreements with local player Sinovac to promote the latter's flu vaccine in 2007 and forming a joint venture with Shenzhen Neptunus for the development and production of another flu vaccine in 2009. A second joint venture established in 2009, with Walvax Biotech, will produce and distribute children's vaccines. **PA**

Tianyin Pharmaceutical Receives Approval from SFDA

Tianyin Pharmaceutical, a manufacturer and supplier of modernized traditional Chinese medicine based in Chengdu, China, has received approvals from the Chinese State Food and Drug Administration (SFDA) to produce Pediatric Fever and Cough Oral Liquid in the dosage form of 10 ml/tube and Antibacterial and Anti-inflammatory Capsules in the dosage form of 0.27 gram/capsule.

According to the company, the annual sales of pediatric fever and cough oral liquid products are approximately US$1.1 billion in China. It estimates that the total annual sales of antibacterial and anti-inflammatory products are approximately US$1.5 billion. **PA**

Sinovac Files Clinical Trial Application for HFMD in China

Siinovac Biotech, a provider of biopharmaceutical products in China, has has filed the application with China's State Food and Drug Administration (SFDA) to commence a human clinical trial for its vaccine against human enterovirus 71 (EV 71), which causes hand, foot, and mouth disease (HFMD). This is the first clinical trial application for a HFMD vaccine that has been submitted in China, according to the company.

Sinovac is independently developing the EV 71 vaccine and will retain full commercialization rights of the vaccine upon approval. Created by Sydney University, the animal model showed cross protection and demonstrated that the vaccine is effective in animals. In addition, Sinovac is preparing to file a patent application covering the EV 71 vaccine.

According to China's Center for Disease Control (CDC) between January 1 and November 30, 2009, the disease has caused more than 400 deaths in the country, where health authorities reported over 1.1 million HFMD infections. **PA**

Special Report

Pharma Outlook 2010

With the economic landscape starting to look rosier as countries recover from the global recession, experts share their views on industry trends and developments for the year ahead.

Cold Chain Efficiency

Bernard Lee,
MD, Procuro Asia Pacific

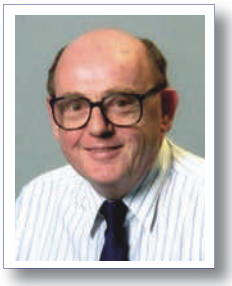
In the past, pharmaceutical cold chain logistics and other perishable cold chain logistics have very little overlap, mostly because of the higher standards and higher prices that the pharmaceutical industry requires and is willing to bear. The picture is starting to change.

First of all, a lot of the same equipment is used throughout the cold chain logistics industry as a whole. What sets the difference is how well the cold chain is enforced through best practices, traceability and compliance monitoring.

Such practices in the cold chain transportation of other perishables continue to improve, and the adaptation of cold chain across other perishables is driving down the cost of best practice in general. We should start to see some cross application of technology in 2010.

A Japan International Co-operation Agency (JCIA) sponsored immunization program recently selected a temperature recorder that is commonly used by quick service restaurants. This was for cold chain compliance monitoring of vaccines that are supplied to Cambodia. They have determined that their chosen unit, which costs less than half of any others that are commonly used in the pharmaceutical industry, is of equal if not better quality and reliability for their purposes. With competition, companies that adapt quickly and remain efficient thrive, and the consumer wins. **PA**

Stepping Up Pharmacovigilance



Dr John McEwen,
adjunct associate professor, University of Canberra

External expenditure on training is one of the easiest and earliest items to be slashed in economic hard times. The economic consequences of the global financial crisis have also resulted in the consolidation of activities, including the regional co-ordination of pharmacovigilance.

For some major companies, this has resulted in the closure of activities in Sydney, Australia in favor of Shanghai, China. The economic upturn will see increased expenditure by companies on Asia-focused pharmacovigilance training in 2010 and beyond. Both commercial organizers and not-for profit societies will be involved, with conferences or workshops that have already been advertised for Shanghai and Hong Kong.

The second development is not a consequence of the economic situation but a growing maturity of regional regulatory agencies. Both the European Medicines Agency and the US Food and Drug Administration are frequently requiring commitments to additional post-marketing pharmacovigilance activities and product-specific risk minimization activities – as a condition for the marketing of new active substances and major extensions of indications.

Regulatory agencies in Asia Pacific will start to demand to be informed of the commitments in Europe and the US, and to receive the results of those activities. **PA**

Increasing Productivity

Yap Swee Lee,
director, Market Development, Asia Pacific, Waters

From an analytical system point of view, technologies that are capable of increasing productivity and reducing operating costs should see greater adoption. Ultimately, these technologies can have a great impact on a company.

Liquid chromatography systems have been an essential tool that is used by the pharmaceutical industry. Sample analysis throughput, reduction of operating costs and environmental friendliness will be key selling points moving forward.

Since the introduction of Ultra Performance Liquid Chromatography (UPLC) technology in 2004, separation science has shifted, demonstrating its capability to meet the requirements of the pharmaceutical industry and has significantly impacted business performance. Expanding UPLC into multiple applications from research to manufacturing will continue to increase the adoption of this technology. **PA**

Advancing Automation

Eugene Yeo,
director, Pharmaceutical Industry South East Asia, Siemens

We are seeing improving business in the Asia's pharma space for the industry automation business. With the major mergers and acquisitions that are taking place today with the Big Pharma companies, it is hopeful that the momentum will continue – driven by increasing demand for quality medicine in the Asian region and new drug developments internationally.

While India and China are both key growth engines, we are also experiencing increasing activity in the rest of Asia.

For example, 2009 has seen a flu vaccine plant coming on stream in Taiwan to meet recent pressing demands. In 2010 we expect a major liquid formulation plant to be coming online in the Philippines. In Singapore, Baxter and Alcon have adopted automation platforms. We should also see more activities in the Process Analytical Technology (PAT) area. **PA**

Raising the Bar in Quality

Christian Wölbeling,
senior director, Marketing & Sales, Werum Software & Systems

Increased Quality Control and the adoption of international standards is crucial for success in the pharmaceuticals industry. Regulatory requirements (eg, FDA) is especially important for exports. Electronic batch recording "right first time" support results in stronger user guidance for improving process and product quality – this is the biggest challenge for Parma.

We should see a rise of PAT in pilot projects. Pertaining to the Quality by Design (QbD)/PAT approach, Manufacturing Execution Systems (MES) manifests itself as a leading solution for process performance management, product quality monitoring and continuous quality verification. QbD is also growing in importance in R&D as quality is vital for the design of new products. **PA**

Special Report

Regional Growth

Dave Grange,
CEO, PPD

As we look into 2010 and beyond, biopharmaceutical companies will continue to expand their drug discovery and development programs in Asia Pacific. This is because of larger patient populations, faster recruitment compared to Europe and the US, and the large, centralized hospitals that Asia offers. We have already seen an increased desire by countries in this region to conduct global trials, which we expect to continue this year.

Governments in these countries will continue to enact regulatory changes to ensure that trials are performed according to good clinical practice and International Conference on Harmonization (ICH) guidelines. Contact Research Organizations (CROs) will support this effort through increased training.

In addition, we will see more inspections than in the past and at earlier stages as a safeguard to ensure ethical and quality standards. In China, for example, improvements in regulatory timelines and intellectual property protection – two of the major challenges to conducting clinical research in the country, will continue as the country places greater value on intellectual property.

We also expect more Western-trained physicians to return to their home countries such as India and China, adding to the pool of experienced investigators that are available in the region. As a result of these measures, companies should become more comfortable working in Asia Pacific and realize that this is a region where they can conduct high quality research. **PA**

Process Optimization

Ulf Nehrbass,
CEO,
Institut Pasteur Korea

From the human genome, the proteome and the transcriptome to Ribonucleic Acid interference (RNAi), each has been an achievement its own right.

My hope for 2010 is to spare the industry yet another "breakthrough". And the chances are good: Much of the hype in the life science community over the last decade has been to accrue functional data beyond a critical limit.

Incorporating aspects of previous breakthroughs, life science has edged towards a more quantitative discipline, gradually becoming more predictable for therapy development. Eventually, much of the current drug discovery paradigm will find itself upended. For example, the identification of effective drugs will be preceding the isolation of drug targets.

Target-free visual approaches already allow for a faster identification of effective drug candidates, which in turn are used to identify their targets in a secondary routine. Imaging, in parallel, allows for target free optimization, saving valuable time. These technologies, many of which are being developed in Korea, will transform our industry. **PA**

Asian Expansion

Dr Tan Chor-Koon,
Pharmaceutical and Life Sciences Industries South Asia Pacific & Korea,
Agilent Technologies

The year 2009 was characterized by muted activity and investments in the pharmaceutical industry in most of Asia, except China. With the economy recovering in 2010, we foresee that activities and investments will start to trickle in.

The big pharmaceutical companies' growth will be slow, as their sales are being eroded by mid-sized companies as well as local generics drugs manufacturers. Big pharmaceutical manufacturers in Asia are experiencing the same Mergers and Acquisitions (M&A) as in the US and Europe. The success with this wave of M&A will come from companies that are working on oncology and Central Nervous System (CNS) drugs, due to their biologic nature being less prone to competition from the generics pharmaceutical manufacturers. Biological drugs will be the strongest growth area for the Big Pharma.

In terms of R&D, the investments from Big Pharma are not reflected heavily in Asia. However, many governments in the region will continue to drive the R&D activities together with the pharmaceutical companies. Many of the multinational pharmaceutical organizations are utilizing the expertise and infrastructure that are found in universities, to conduct R&D activities. This trend should continue and expand with the collaboration between state-funded research institutes and the private industry. **PA**

Enquiry code: 101E01

Digital Pathology and Biomarkers Help Pave the Way to Personalized Medicine

Advances in biomarker technology are aiding researchers in identifying the right treatments – for the right patient.

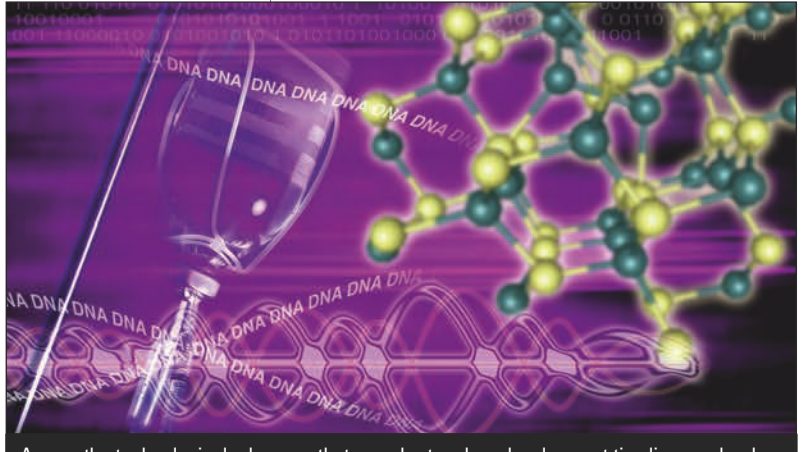
Christopher Ung,
VP,
Strategic Business & Operations, Oncology,
Quintiles

The biopharmaceutical industry is adapting to shrinking pipelines, increased market access barriers, significant financial strains and advances in technology. Companies must employ certain tools to bring life-saving medicines to market sooner and remain competitive in the rapidly changing arena of drug development.

Among the technological advances that can shorten drug development timelines and reduce the overall complexity of conducting clinical research, digital pathology and advanced biomarker development stand out. These areas hold the potential to not only reduce costs and timelines, but also deliver more targeted, and more effective therapies to patients.

Targeted Treatment

In 2008, researchers made a breakthrough when studying the V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) gene – a molecular triggering gene that transforms a protein that is implicated in several types of cancers. They identified a mutation within this gene as a negative predictor for well-known oncology treatments, particularly with regard to a class of drugs called Epidermal Growth Factor Receptor (EGFR) inhibitors. This data proved to be compelling, as patients with the mutation have little chance of responding to this class of drugs. About 35 to 40 percent of colorectal cancer patients have these mutations. By excluding these patients, researchers can spare them any potential side effects and focus efforts on treating patients with wild-type KRAS.



Among the technological advances that can shorten drug development timelines and reduce the overall complexity of conducting clinical research, digital pathology and advanced biomarker development stand out.

Today, the KRAS mutation assay is used globally to select relevant patients for treatment with EGFR-targeted therapies. The American Society of Clinical Oncology and the National Comprehensive Cancer Network have recommended that all patients with metastatic colorectal cancer be tested for mutations to the KRAS gene.

The European Medicines Agency (EMEA) led this movement by officially recommending that only KRAS-wild-type patients be treated EGFR monoclonal antibody therapies. These recommendations further validate the role of mutation assays and biomarkers as cornerstones of personalized medicine and targeted therapies.

The KRAS breakthrough is an example of a molecular marker that is used to match the right patient with an approved targeted therapy, since virtually no patient who is harboring mutations in the KRAS gene responds to EGFR monoclonal antibody treatment. The targeted selection of patients is a role that biomarkers offer and will be explored by organizations that are developing targeted therapeutics in oncology.

Cover Story

Additionally, researchers are using biomarkers as a Pharmacodynamic (PD) tool to help to assess the efficacy of the therapeutic agent. This approach allows researchers and trial sponsors to understand how the drug is working and to do so earlier in the process. Multiple biomarkers are frequently interrogated to gain an understanding of the pathways that are being activated or inhibited in the cancer cell.

These panels of biomarkers are often a leading indicator of potential combination options either with chemotherapy or additional targeted agents. For instance, the Phosphoinositide 3-Kinase (PI3K) pathway is commonly invoked by tumor cells as a survival pathway.

By validating biomarkers that probe for loss of phosphatase and tensin homolog (PTEN) by Immunohistochemistry (IHC), assess amplification of the PI3K gene by Fluorescence In Situ Hybridization (FISH), or by evaluating the PI3K mutations by Reverse Transcription Polymerase Chain Reaction (RT PCR), developers of targeted agents against PI3K can assess early the efficacy of their PI3K inhibitor.

Then, when combined with biomarkers for another pathway, such as mammalian Target of Rapamycin (mTOR), for example, the accumulated data can provide insight into the value of combining PI3K and mTOR inhibitors for a particular tumor indication.

Digital Capture

Oncology biomarker work commonly involves tissue, specifically the stains on patient tissue that highlight the presence of a certain protein or genetic target. Digitally capturing this information allows an investigator to leverage the richness of data that is contained within the patient's tumor morphology.

Today's technology allows researchers to digitally capture an entire slide, share it almost in real time and then mine the image for quantitative and qualitative data. The ability to look at digital images from any investigative site worldwide, in essence, allows a researcher to use his or her computer as a microscope. It also eliminates issues that are associated with transporting and storing human tissue, and makes sample images available instantly, thereby providing cost savings and decreasing the overall development timeline.

The actual image analysis of tissue samples offers potential in the area of oncology even in its current embryonic stage. Fundamentally, image analysis can help to standardize the interpretation of IHC stains. As opposed to just looking at a picture and making an estimated guess as to how much protein is present, for example, digitized images enable pathologists to use sophisticated software to do this work in a quicker and more accurate manner.

The advent of personalized medicine pushes the need to develop more effective biomarkers, both for patient selection and for pharmacodynamic analysis.

Clinically, algorithms such as the Human Epidermal growth factor Receptor 2 (HER2), Estrogen Receptor (ER) and Progesterone Receptor (PR) have received regulatory approval to assist in patient diagnosis to help to identify those patients who might respond to a therapy, versus those who might not. These algorithms have the potential to limit the variability of interpretation among pathologists.

The use of digital image algorithms can also be extended to clinical trials. The ability to identify a specific patient population can help to reduce the overall time that is needed to conduct a trial. By knowing exactly what to look for on a slide sample, researchers can immediately narrow the potential pool of patients to a specific genotype or protein level.

Biopharma as a whole is beginning to embrace this emerging technology, and many organizations have established digital pathology networks with in-house scientists who are tuning digital algorithms to analyze samples.

It is conceivable that these activities may lead to an improved personalized medicine environment in which patients are selected more accurately to receive specific targeted therapies. Clinical pathologists will be able to furnish patient results to clinician colleagues with greater confidence, underpinned by algorithms that are designed to chase out confounding subjectivity.

Finally, a centralized digital pathology network in which all image analysis and readings are conducted in one location – using a standardized process – eliminates variability, increases accuracy, provides data storage security and enables the near real time dissemination of vital image data. By transferring high-resolution images digitally, researchers will no longer need to ship physical specimens. This is particularly beneficial in countries that prohibit the export of human tissue, such as China.

The targeted selection of patients is a role that biomarkers offer and will be explored by organizations that are developing targeted therapeutics in oncology.

As China continues to expand its involvement in clinical research, using digital pathology instead of traditional glass slides decreases development timelines by enabling pathologists anywhere in the world to analyze images and collaborate in real time. Working with an organization that has invested in a robust, scalable and secure network allows drug developers to reap these benefits.

Substantial thought has to be invested in such a network, but once it has been setup and deployed on a global basis, the drug developing organization can begin harvesting the benefits of expanded collaboration and reduced shipping and logistics costs. Best practices may also emerge. For example, digital pathology can enable the ability to use the best pathologist in the organization for a particular application (eg, a certain type of tumor or pathway).

Transforming Cancer Research

So, what does the biomarker and digital future look like? The evolution of biomarker and digital pathology technologies have the potential of enhancing the intelligent design of targeted oncology clinical trials while minimizing toxicity in patients. Meanwhile, the advent of personalized medicine pushes the need to develop more effective biomarkers, both for patient selection and for pharmacodynamic analysis. Therefore, the validation of these biomarkers becomes central to the success of deploying them in global clinical trials.

The utility of digital pathology and image analysis has the potential to assist in the successful use of these biomarkers in large, global Phase III trials. In the future, it may be possible to select the right patient with the optimal biomarker and to do so accurately with a helpful boost from digital image algorithms.

This can serve to increase the efficacy of the therapeutic agent and to screen out patients who are not likely to respond to a particular drug. At the same time, costs can be reduced by eliminating unnecessary clinical trials, shrinking development times, and avoiding the unnecessary treatment of patients who are not likely to respond.

In addition, by leveraging biomarker information, researchers can ascend to the next rung of patient treatment – understanding how to combine therapies. Through combinations – for example, chemotherapy plus a targeted therapy or two targeted therapies – researchers can begin treating patients by intelligently hindering the pathways that assist the tumor cell and activating the pathways that control it.

The patient will no longer simply be a "breast cancer" patient or "colon cancer" patient receiving routine prescriptions of the "typical" chemotherapeutic and targeted therapeutic cocktails. Instead, biomarker researchers will have the ability to decipher a pathway map of the patient and then rapidly identify the right combination of drugs to treat each individual patient – often in a blockade fashion to thwart the tumor cell's strategies – and to do so in a more cost-effective and time-effective manner.

Pharmaceutical companies recognize the potent power of biomarkers and have embraced the latter's utility in drug development. The recognition of digital pathology advantages is likewise developing rapidly. Regulatory agencies are strong advocates for biomarkers in drug development and have also initiated forums to highlight the potential uses of digital pathology and image algorithms for drug development.

These initiatives map a journey for cancer research and drug development, and the industry is committed to getting the best treatment to patients. Already, new chapters are appearing in the biomarker lexicon as investigators ponder on how to bring life and utility to emerging technologies. There is a desire to gain control of gene expression and to hunt down circulating tumor cells. And in line with the goals of personalized medicine, this is being carried out to achieve optimal patient outcomes, increased efficacy, decreased risk and reduced side effects for patients. **PA**

Enquiry code: 101E02

Drug Discovery

Mass Spectrometry: Processing Power

Rapid advancements are pushing the technology towards higher productivity and greater precision.

John Moncur,
director
SpectralWorks

Many of the recent developments in Mass Spectrometry (MS) have been focused on promoting the mass spectrometer as both a universal and a highly specific detector. Although these seem to be diametrically opposed objectives, such is the flexibility and ease of use of modern MS instrumentation that these two functions are a reality.

Quality Improvement

The accessibility of modern mass spectrometry is approaching the "black box" level. Many believe that the previous limitations of MS such as speed, resolution, dynamic range and ease of use have all been eradicated. But while progress has been made in these areas, such problems still arise from time to time.

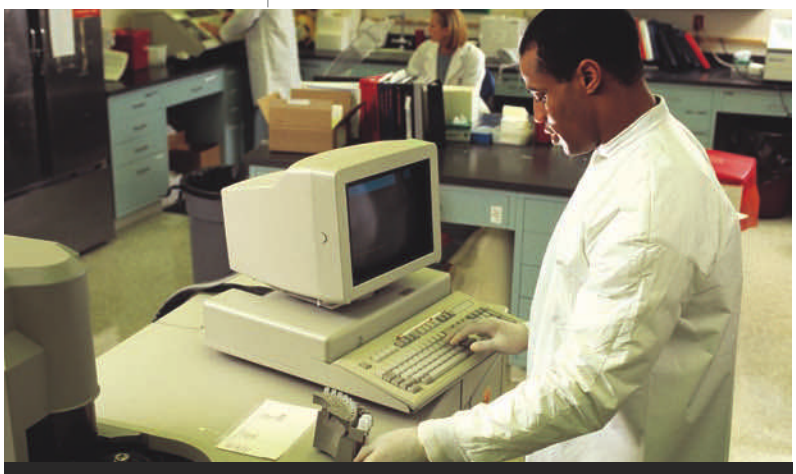
Users who are familiar with Gas Chromatography with Flame Ionization Detection (GC-FID) are now able to use Gas Chromatography Mass Spectrometry (GC-MS) routinely. While the FID detector has a wide dynamic range that can extend over seven orders of magnitude, GC-MS can be limited to four or five.

This limitation arises from a combination of a number of instrument characteristics, including ion source and detector limitations as well as potential limitations in the mass analyzer (such as an ion trap) itself. Different ionisation processes, such as chemical ionization for GC-MS and electrospray for Liquid Chromatography Mass Spectrometry (LC-MS) can be even more limited and may also be compound dependant. It is therefore important to be aware of these limitations when developing methods, particularly where quantitation is involved.

The "need for speed" is driven by the progress that has been made in the front-end technologies, such as GC-MS and LC-MS, as well as the requirement to extract as much information from a single sample injection in the shortest period of time.

The provision of MS instrumentation is still seen as a heavy financial investment and it is natural for the buyer to want to see a significant return on that investment – by running as many samples as possible. As chromatographic methods and technology are developed to provide higher resolution and sample throughput, the resulting peak widths are reduced.

Much has been written on the optimum data sampling rate for the accurate determination of peak areas but it is generally accepted that the faster the sampling rate, the more accurate the peak integration will be. Ultrafast GC, Ultra High Performance Liquid Chromatography (UHPLC) and Two-dimensional Gas Chromatography



The "need for speed" is driven by the progress that has been made in the front-end technologies, such as GC-MS and LC-MS, as well as the requirement to extract as much information from a single sample injection in the shortest period of time. (Source: SpectralWorks)

(GCxGC) are examples of front-end techno-logies that are pushing up the data sampling rates that are expected of any mass spectrometer.

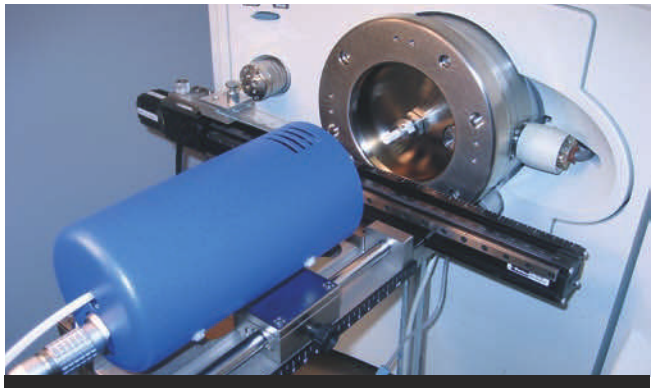
Conventional HPLC is able to provide peak widths of the order of 2-3 seconds Full Width at Half Maximum (FWHM) whereas UHPLC can now offer peaks in the order of 0.7 seconds FWHM. Ultrafast GC can produce peak widths of around 0.1 seconds FWHM. In order to maintain the accuracy and precision of peak integration, the mass spectrometer cycle time must be reduced in order to get sufficient numbers of samples across such narrow peaks. Given that many MS instruments, such as the LTQ-Orbitrap and the Quadrupole Time-of-Flight (Q-ToF) technologies are now providing routine high resolution information, there is a requirement for faster data acquisition rates for the MS itself. Data sets from a single injection are approaching Gigabit proportions.

The provision of MS instrumentation is still seen as a heavy financial investment and it is natural for the buyer to want to see a significant return on that investment – by running as many samples as possible. (Source: SpectralWorks)

Computing Capability

If the possibility of Tandem Mass Spectrometry (MS-MS) acquisition modes is introduced, the amount of data can be overwhelming. The development of faster electronics, faster and more powerful computers and greater data storage capability is barely keeping pace with this. Without such development, much of today's MS analyses would be impracticable.

Mass spectrometry has been a powerful tool and it is the development of readily available digital processing capabilities to match, that has made MS accessible. The development of ionization techniques, such as Direct Analysis in Real Time (DART) and Desorption Electrospray Ionization (DESI) coupled with improvements in scope and sensitivity of existing ionization processes, is expanding the applicability of MS analysis.



The development of ionization techniques such as Direct Analysis in Real Time (DART) coupled with improvements in scope and sensitivity of existing ionization processes, is expanding the applicability of MS analysis. (Source: KR Analytical, UK)

The development of "ambient" ionization techniques, described by Cooks – where ions are created outside the MS instrument to produce mass spectral data from samples in their native state – can allow real time analysis and reduces possible artefact generation and sample breakdown in the harsher environments of the more common ionization processes. These techniques have been used to perform biological tissue imaging by mass spectrometry as well as a variety of other applications including environmental and forensic studies.

The coupling of Ion Mobility Spectrometry (IMS) techniques, such as with the Synapt HDMS mass spectrometry system, adds another dimension of separation – which allows the differentiation of molecules based on size and shape prior to coupling with mass spectrometry. This increased information content is compatible with Ultra Performance Liquid Chromatography (UPLC) timescales, which allows the greater characterization of samples.

Instrument vendors are keen to provide a "Solution" to a problem as the opportunity for cross selling of products is great. This can include everything from the sample preparation consumables and equipment through to the software to provide statistical reporting of study results. However, the MS instrument may only be a small component in the overall solution. Looking at the field of Metabolomics, the mass spectrometer is an important piece in the analytical jigsaw, but who is buying them? Biologists, zoologists, clinicians, statisticians or accountants? There seems to be a declining focus on chromatography and mass spectrometry professionals. Conversely, it is important for the chemist who is specializing in mass spectrometry to have a firm understanding of the end use of the data that is produced, to ensure that it is "fit for purpose".

The developments in mass spectrometry have made it more accessible and it is now a powerful tool to many researchers. However, whatever the progress that is made, it will remain as only a part of the solution that requires a well balanced approach from multidisciplinary research groups. Developments are only of benefit to the wider communities when they are readily adopted. While word of mouth and networking are important, the majority of the market still relies on key individuals providing peer reviewed contributions to quality publications. This provides the "proof of concept" that others will be able to adapt and adopt. **PA**

Enquiry code: 101E03

Clinical Trials

Facilitating Data Management in Clinical Trials

Organizations are harnessing technologies such as Electronic Data Capture (EDC) to improve the efficiency of clinical studies.

Nick Giannasi,
VP of Strategy, Oracle Health Sciences;

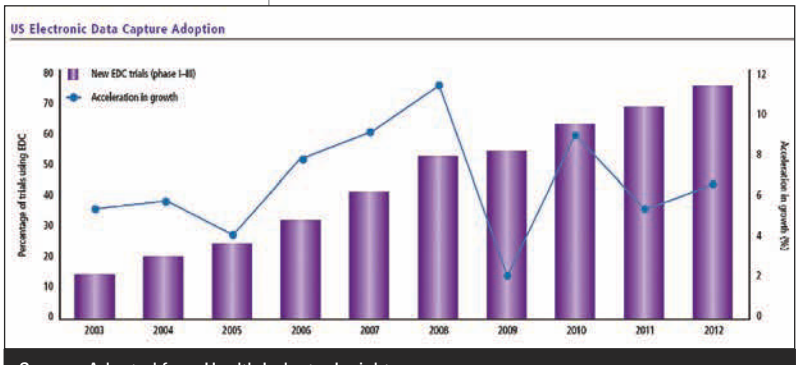
Yashi Kant,
VP, Oracle Health Sciences, Asia-Pacific

The Internet and e-technologies have become an integral part of business in most sectors, but have taken time to gain traction in the clinical trials arena. As the industry faces challenges and further consolidation, companies are increasingly embracing technology as a lever to differentiate themselves, boost productivity, and succeed.

Dealing with Data

In the pharmaceutical industry, the emergence and acceptance of Internet-enabled technologies such as Electronic Data Capture (EDC), have transformed clinical development practices – efficiently supporting faster, larger, and more complex trials.

Current industry projections estimate that the technology is now used in approximately 50 percent of all clinical trials. Companies are increasingly leveraging this technology and other tools to power global trials, and benefit from the ability to analyze incoming data and performance metrics in real time. The availability of such data supports more rapid decision-making and provides the agility to make the necessary adjustments during ongoing trials.



Source: Adapted from Health Industry Insights

With the increased adoption of the technology, market expectations are high. A more technology-fluent user base is demanding richer features, ease of use, and flexibility within trial settings. Global usage also requires availability and scalability. Furthermore, there is a growing acknowledgement that this technology represents only a subset of the critical aspects of the overall data value chain, highlighting the need for a fully integrated e-clinical ecosystem. Such an integration of EDC and other eClinical systems will provide a holistic view across trials and data sources and minimize process and infrastructure redundancies.

Due to the increasingly prevalent use of EDC coupled with industry outsourcing trends, the role of an "in-house" data manager has changed considerably. Further removed from the daily discrepancy resolution routine, these individuals are now charged with program-level oversight responsibilities – including tracking the progress of work being conducted by third-party Contract Research Organizations (CROs), and sometimes across multiple organizations on several studies.

While skills in the core data management systems are still vital, better tools are necessary to provide oversight-level data in real time, and productivity and performance metrics are paramount to understanding and measuring this environment. While the ongoing global expansion of trials presents new opportunities, it increases the pressure and the demands that are placed on EDC and Information Technology (IT) infrastructure and support resources. The growing prevalence of global site users and outsourcing practices have transformed clinical trials into an around-the-clock operation.

No Time for Down-Time

This "always on" business model creates a technical support dilemma. Given the 24/7 availability requirements to support the global trial environment, there is no opportune time to schedule maintenance and perform repairs.

Furthermore, in the event that a technical problem that affects system availability does occur, all sites that are using the technology platform can potentially be affected. For example, a pharmaceutical company that is running 300 trials concurrently, might in the worst-case scenario, have to suspend workflow on all trials until access to the system can be restored.

Given the implications of this example, companies are focusing on issues such as infrastructure/server redundancy, backups, and failover. There is an absolute dependency on IT support and service levels to ensure business continuity in running clinical trials. This reality has been an internal hurdle for many organizations that are seeking to implement the system, and some have opted to outsource.

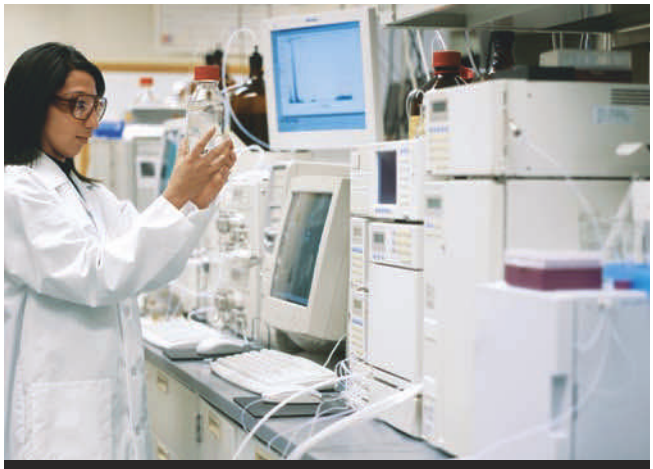
Similarly, since its use extends to site staff as well as CROs and business process outsourcing providers, the exponential growth of user populations has led many organizations to rethink their

While the ongoing global expansion of trials presents new opportunities, it increases the pressure and the demands that are placed on EDC, IT infrastructure and support resources. (Source: Oracle)

EDC support strategies. Both end-user training and ongoing helpdesk support are critical to success.

Vendors are moving into this space specifically to handle initial training, arrange Internet connectivity around the world, and negotiate Internet service provider agreements. They also

Clinical Trials



Instead of a single analysis after the trial is completed, trials today require multiple sophisticated data cuts and ongoing analyses (Source: Oracle)

provision and track hardware when necessary, and provide all-hours helpdesk services in multiple languages.

Trials have evolved significantly over the past several years. Historically, the traditional trial model followed a natural, sequential pattern in which companies would collect data over the course of the trial. When the trial is completed, the database would be locked, to carry out analyses and assemble a candidate submission.

Clinical trials today, however, are more complex. The advent of EDC enables earlier data review, and it has also helped to advance new trial designs that rely on such early data availability. Instead of a single analysis after the trial is completed, trials today require multiple sophisticated data cuts and ongoing analyses. The availability of data from EDC helps to facilitate such "soft-lock" processes, effectively simulating a subset of the traditional end-of-study procedures with interim data.

This mid-study process can occur multiple times during the trial for safety monitoring boards, submissions, or interim reviews. However, utilizing this type of rolling lock system consumes more resources than the traditional process. So, while EDC enables resource savings for traditional discrepancy management activities (as projected), this trend for more complex trials and process changes, introduces added complexity and resource demands to support a study.

The use of adaptive trials is also increasing, which requires support for real time insights and a variety of mid-trial modifications for dynamic response to changing circumstances.

Complex trials are also being leveraged strategically to optimize resources and productivity given the constrained financial climate, budget cuts, and pressure to run fewer trial programs. To meet trial quotas while fulfilling project needs, companies can opt to run multiple studies within a single trial. For example, within a single oncology trial, there may be six separate study populations, each based on a different tumor type.

Data Integration and Interoperability

EDC is just one aspect of the eClinical ecosystem. There are many systems that are employed throughout the clinical development process for data acquisition, data analysis, trial management, and reporting. As the volume of data from all sources increases, the need for an intelligent aggregate data storage environment becomes imperative.

One such system – the Life Sciences Data Hub – enables access to all trial data from a single location. This reduces the time and effort that are required for study reporting milestones while providing the ability to accurately track and reconstruct complete reporting data sets and outputs.

While there are a multitude of available software platforms that are designed to manage various aspects of clinical trials, most of these disparate systems work independently of one another, unable to communicate or share information. Additionally, sponsor companies may use separate, independent vendors for each IT system, particularly if they seek to employ "best-of-breed" options for every product type. When overlap does exist between applications but identical data must be entered into them independently, the issues of redundancy and inefficient use of both time and resources are compounded.

Going forward, interoperability will be a key factor in realizing maximum possible results using eClinical systems, allowing records to be linked and shared, and eventually improving efficiency and reducing overall costs. Industry standards will evolve to make disparate platforms interoperable and less proprietary. The Health Sciences Suite platform – a fully integrated suite of eClinical applications – is being developed that will also be able to extend to applications from other vendors.

The industry is changing rapidly and organizations across the pharmaceutical spectrum are dealing with many of these pressures, while trimming operating expenses, and establishing cost-effective and efficient working practices. The eClinical transformation offers an opportunity to maximize the value of clinical trials, improve pharmaceutical development efficiencies and ultimately provide patients with timely, new, and improved treatment options.

There will be short-term challenges to be overcome in the process of continuously adapting to new technologies and gaining acceptance of new ways of working. It is therefore critical to weigh technology investments against both short- and long-term objectives. **PA**

Enquiry code: 101E04

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

Different countries posses varying characteristics that affect the selection of business models for outsourcing activities.

Frank Floether,
VP Business Development Asia Pacific (2004-2008), Johnson & Johnson

One of the key decisions that needs to be made by a company that is aiming to establish a presence in Asia, is to choose the optimal business model. Each model will perform differently under different conditions. Any given project or R&D area might lend itself to a certain model. So the model of choice will be determined mainly by the nature of the activity.

Mode of Operation

For example, clinical trials may be safely outsourced to a reliable vendor, whereas full scale Good Manufacturing Practice (GMP) chemical and formulation development requires an investment in equipment and staff and be operated to Western GMP standards. The decision on the model is likewise determined by:

- Country (China vs India vs Singapore);
- Nature of the company;
- The company's objectives and long-term goals;
- The degree of flexibility needed;
- Intellectual Property Rights (IPR)
- Risk tolerance;
- Available budget;
- Existing engagement in the respective country

The model of choice is mainly determined by the nature of the activity.

MNCs have tried a number of different approaches. The following business models have emerged as the main options:

1. Captive R&D Center

Key Features:

- MNC operates at a fully owned site
- Large investment and limited flexibility
- Full control over IPR, talent and know-how

This model represents the most serious and committed presence in any offshoring destination. It is however vulnerable to problems with planning and construction permissions, red tape issues in general and has limited flexibility.

One way of mitigating these challenges might be to start with a joint venture in order to obtain assistance from a local partner on how to operate in the country. After the joint venture contract and relationship expires, the MNC takes over or alternatively buys out the partner.

2. Partnership

Key Features:

- Partnering with a local provider who acts on behalf of the MNC and returns the project to the MNC after the respective work is done
- Moderate investment and greater flexibility
- Easy access to local talent
- Limited IPR control

This model can help to ease capacity constraints, and leverages on the partner's experience in managing local red tape – however intellectual property could become compromised.

Drug Development

3. Build-Operate-Transfer (BOT) Model

Key Features:

- After forming an alliance with a local company, the latter hands over facilities and workforce at an appropriate time.
- Investment is spread out over time.
- Fast access to local talent and managing red tape via local ally.

There is good track record of this model in other industries. It allows the MNC to test local methods of getting work done before undertaking the risk of setting up its own full-fledged center.

4. Third-Party/Vendor–Based Outsourcing

Key Features:

- Outsourcing of selected activities to third party providers
- Almost zero investment
- High degree of flexibility
- Know-how transfer and IPR risk limited

This is the least risky and most careful approach to offshoring, particularly useful for well-defined, less complex activities (eg, stability testing). However it is also limited in insights regarding the respective country and is limited in terms creating a strategic presence.

In practice, there are also various kinds of hybrid models. An MNC might migrate in two stages, eg, from a vendor-based to a captive business model.

The alternative to these four options is the "wait-and-see" approach. This is not considered a real model by definition and does not describe a concrete course of action with respect to offshoring. Waiting and holding off from any involvement or extension of involvement until conditions improve, bears the risk of lost opportunity.

The location and city selection is an important aspect as well. Key factors are eg, the ability to attract talent, cost aspects (land, workforce), clustering effect, proximity to MNC's headquarters, proximity to authorities, etc.

In China, Shanghai is the city of choice for R&D centers, followed by Beijing (largest number of institutes and universities), Guangzhou, Tianjin and Hangzhou. In India, the focus is on the Mumbai / Pune area, Hyderabad and Bangalore.

Making a Choice

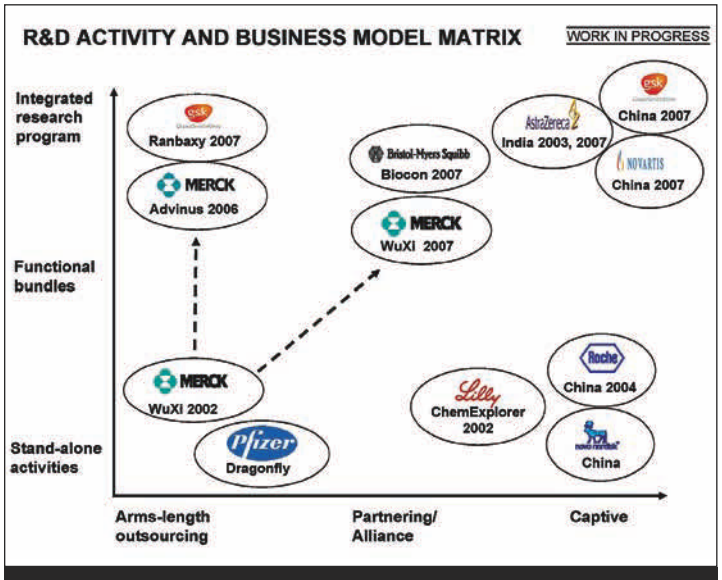
In terms of pharmaceutical offshoring, China and India generally require different business models. The characteristics of each country translate into certain preferences for the choice of the operating model.

In China, the preferred business model seems to be the captive center. The existence of a captive site indicates an MNC's commitment. This is more than just symbolic as it encompasses visibility, establishing the brand name with patients, doctors and authorities, and eventually translating into sales.

Chinese officials like to see technological advancements in their country – which may be best achieved by a captive center. It is viewed as one of the ways to assist Chinese R&D institutions and vendors to move along their learning curve by demonstrating international best practices and inspiring local R&D providers. This model is favored by Chinese officials and may be instrumental in influencing regulatory and pricing policies as well as tighter IPR protection.

Pertaining to chemical and pharmaceutical R&D in India, which is currently more advanced and mature than China's – the vendor-based, uncomplicated, "arm's-length" outsourcing model is more suitable. For example, by offshoring some of its "excess" leads, an MNC can quickly and cheaply ease its capacity constraints and leverage India's wide variety of vendors, ie, both the large integrated domestic players and the myriad of ambitious smaller vendors.

It might be useful to illustrate some of the activities of selected MNCs, in particular with regard to their R&D business, by clustering them according to the business models discussed.



Schematic display of various business models in China and India. (Source: McKinsey)

A number of wholly owned R&D centers in China are operated by:

- GSK with a total more than 2,000 employees including an over-the-counter R&D center in Tianjin);

• AstraZeneca has a US$100 million center in Wuxi, Jiangsu province. The company is also investing US$14 million in Wuxi PharmaTech;

• Novartis has a US$100 million R&D center in Shanghai;

• Roche has one of its five R&D centers in Shanghai;

• Novo Nordisk has a US$10 million R&D center in Beijing;

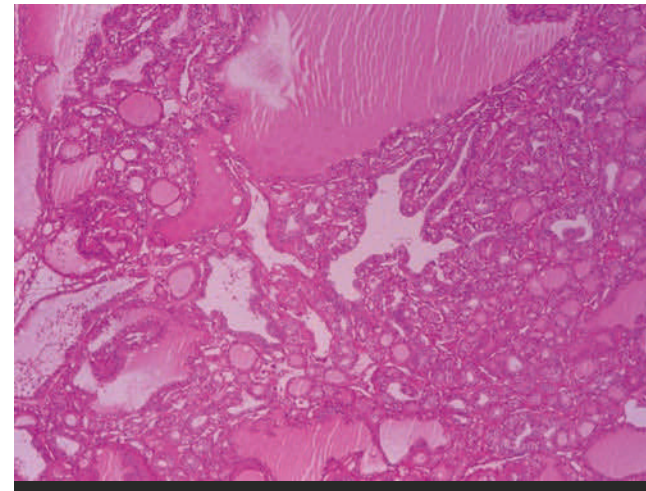
• Eli Lilly is an example of an exclusive partnership (with ChemExplorer);

• Others are Schering-Plough, Merck and Johnson & Johnson (joint venture Xian- Janssen).

Some of the most reputable Chinese vendors for vendor-based outsourcing are WuXi PharmaTech, ChemPartner, Medicilon, Shanghai Genomics, Dragonfly, Frontage and BioDuro.

In India, wholly owned R&D centers are associated with Altana, growing out of a joint venture with Zydus Cadila, setup in 2000 for API and clinical research. Novartis owns its International Clinical Development Center in India.

The applied business models are many, mostly by strategic partnerships, acquiring local companies, and increasingly by setting up wholly-owned R&D subsidiaries.



Value in offshoring lies not just in cost savings but also in the faster development of new compounds and in penetrating new markets.

AstraZeneca set up a world-class R&D centre in Bangalore 2001. Sanofi-Aventis is carrying out major R&D in several therapeutic areas in its own facilities. Johnson & Johnson's Analytical & Pharmaceutical Development Center for its pharmaceutical franchise is located in Mumbai.

Most MNCs maintain partnerships at various levels with Indian domestic companies and Contract Research Organizations (CRO) as well as performing API and drug product manufacturing in the country at their own plants or within a partnership.

Merck is an example for maturing its partnerships with Advinus and Nicholas Piramal in India and WuXi in China from simple outsourcing in the beginning, into preferred strategic partnerships later on.

Cross-Cultural Considerations

In terms of working with Asian partners, what works in North America and Western Europe may not necessarily work in Asia. Likewise, what holds true in one Asian country may not necessarily be valid in another. This applies to both work-related subjects and to cross-cultural behaviour.

Asian partners generally have a bold "can do" mentality combined with ambition and an eagerness to learn. They are enthusiastic about "proving themselves" and have hard-working employees.

On the flip side, this attitude has sometimes resulted in the "no problem" problem, ie, underestimating the complexity and difficulty of problems or the time that it takes to complete projects.

In particular with partners who have not been exposed to collaboration with Western companies before, the occasional "wait-and-see" mentality can occur. This eventually often leads

Drug Development

to – at least in the settling-in phase of a collaboration – reduced efficiency.

While most of the scientists in India are well-educated, many have a background in pharmaceutical generics only. This means that it will take time to get them used to the new standards that are related to New Molecular Entity (NME) development.

A golden rule is to hear ≠ to understand ≠ to agree ≠ to execute ≠ to make execution repeatable and sustainable.

There are a number of steps that can be taken:

- Training: not just to teach, but to demonstrate before and on the job;
- Helping Indian / Chinese management structure to adjust to employee turnover, which is generally much higher than in the West;
- Make provision for sufficient internal resources for control/ coordination/training;
- Try to predefine the format, structure and expected content of any report in detail;
- Seed Asian organization with expatriates, at least for the start-up phase;
- Work on personal relationships and build trust to reduce cultural and hierarchical barriers;
- Do not rely solely on trust – proactive checks are helpful to avoid surprises;
- Meticulous project planning/tracking;
- Clearly define Rest and Recreation (R&R);
- Be patient;
- Ensure that concrete answers are given.

• China

In China there is little experience in development of NMEs (even less than in India). A Western company would normally require a broker or local affiliate to facilitate interaction with local suppliers and to overcome language and political barriers.

Typically, Chinese suppliers/companies are not responsive to direct enquiries. The use of a local MNC affiliate can aid in working through local issues such as language, laws, politics, etc. Language in China is still a constant barrier, especially in partnerships that rely on trust. Chinese returnees who are employed by the potential partner can be useful in facilitating contact and collaboration.

It is sometimes necessary to have local interpretations of national laws. It is also good to know is that local leaders can influence the speed and extent of development in their respective province or city. Almost unavoidable is the need to work with Chinese government to facilitate any business processes.

Chinese returnees who are employed by the potential partner can be useful in facilitating contact and collaboration.

It still seems that with the right connections – termed as "Guanxi", one can get things done more easily in China. The entry into the World Trade Organization was supposed to make China more of a rule-based system – where guanxi would have far less influence – and also improve its legal system to make its rules easier for companies to understand. Yet guanxi so far remains important in China.

In China, formality is an issue. Local partners do not always like the accompanying paperwork that comes with manufacturing. Although government bureaucracy is familiar to Chinese companies, the production of internal documents, follow-up reports, and regulatory approval documentation often do not receive the same level of attention.

• India

Success in India (and China) may be achieved if extensive, coordinated, consistent and prolonged cross-functional resources are provided by the MNC and if the latter is truly partnering with the Indian company of choice. Cost savings may only be realized after start-up issues get resolved and only if the potential supplier or local affiliate becomes fully operational – a timeframe of typically more than a year.

In India, there is fierce competition between companies to hire, train, and retain skilled scientists/employees. Company loyalty is low and it is common for employees to "job hop". Government labor regulations can make it difficult to downsize or close down plants or R&D units. Inefficiency remains an issue – managers are spending an average of 14 percent of their time in dealing with government regulations, compared to eight percent in China.

The Indian government is offering limited financial incentives to pharma companies for investments although there is an increasing number of tax free zones that are being established throughout the country that provide tax relief.

In China, the preferred business model seems to be the captive center.

There are differences between different Indian states. There is growing development in the number of industrial parks, often located in tax free zones, resembling the Chinese model.

The infrastructure in India is still weak compared with that of the West and also with Chinese urban areas. This pertains to road, rail, traffic and airports. Outages in electricity and the water supply are also common. The majority of companies have their own generators. The Indian government has launched programs to invest in infrastructure.

Legal concerns with IPR and confidentiality are not as dominant compared to China's. India is multilingual and multicultural (Hindus, Muslims, Sikhs, etc). The official languages are Hindi and English. The culture values education and traditional family values. Foreigners need to be sensitive to religious or social differences. The caste system still plays a significant role in politics and business. Local decisions are made by local state government.

Benefits and Constraints

The pharmaceutical industry entered into the offshoring business later than many other industries. Pharma stands to benefit from such the opportunities that this business activity presents, since the real value lies not just in cost savings but also in the faster development of new compounds and in penetrating new markets.

The global pharmaceutical industry is embracing offshoring and its general expansion towards Asia, ie, to potential markets and low-wage powerhouses like India and China. The reality of shrinking profit margins, drying pipelines, patent expirations, intense generic proliferation and increased R&D costs have made offshoring an attractive strategy.

R&D activities in particular, are a focus of MNCs. Next to conducting clinical trials (which make up 60 to 80 percent of a NME's development costs) and API related activities such as chemical process research, increasingly, full end-to-end R&D activities are being set-up by MNCs in Asia. The applied business models are many, mostly by strategic partnerships, acquiring local companies, and by setting up wholly-owned R&D subsidiaries.

MNCs are also wary of offshoring sensitive and vital operations. There is low tolerance for errors; simple mistakes can compromise results, or even harm patients, resulting in massive and expensive liability.

On top of this, the cost of an unsuccessful partnership is more than just a financial issue, since the company loses crucial time and the opportunity of investing elsewhere. In offshoring (by outsourcing to a third party) there is also a loss of partial control to the provider.

Poor communication can lead to problems with quality and can result in delays. There are also concerns about intellectual property. Working across multiple languages and time zones adds to the complexity.

Nevertheless, given the objective constraints in the pharmaceutical industry, globalization and the importance of emerging markets, offshoring and expansion towards Asia is unavoidable, regardless of the means and business model.

The delivery of offshoring benefits requires sustained investment and the development of management experience. In particular, it is necessary develop endurance and adaptability to cross-cultural differences – in line with the pace of capability development in individual geographic Asian environments.

The offshoring of both R&D and manufacturing and other types of core and non-core competencies is becoming an integral component of sustaining profit levels.

There are few major pharmaceutical companies that do not already have pilot programs in place or plans to offshore sizeable components of their operations. Offshoring is expected to increase by 16 percent annually, driven by robust increases in the augmentation and relocation of both back-office and core processes. **PA**

Enquiry code: 101E05

Planning for Success

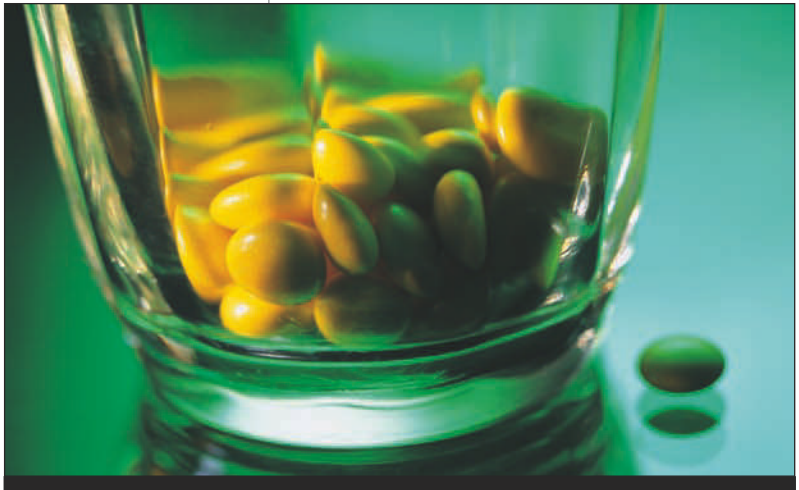
A pathway to obtaining US FDA approval for developing, manufacturing and commercializing generic drugs.

Pedram Alaedini,
President and CEO,
Primapax Biopharma

The pharmaceutical industry is evolving rapidly. More companies, scientists, engineers, and entrepreneurs are establishing contract manufacturing organizations, and developing new and generic drugs. They are searching for better or less expensive raw materials and finished products, and creating consulting and contract research organizations to service the global pharmaceutical industry.

In countries such as China, Poland, Korea, Vietnam, India, Turkey, Brazil and Iran, individuals are in the process of developing generic and new drugs and are submitting their first Abbreviated New Drug Applications (ANDA) to the US Food and Drug Administration (FDA). This is in the hope of receiving timely approvals and entering the lucrative US pharmaceutical market.

Although highly motivated and learning quickly, many of these individuals do not have sufficient experience in the pharmaceutical industry and are not entirely familiar with the requirements that are set by the US regulatory agencies.



Quality by design means developing a product and a manufacturing process that will ensure that the product consistently attains a predefined quality at the end of the manufacturing process.

On the other hand, in order to reduce costs or improve quality, many US companies are in search of partners in other countries to outsource the former's manufacturing, testing, or product development activities. These companies usually become frustrated by their inability to locate appropriate partners or may face difficulties during the transfer of technology.

This is perhaps to some degree due to the companies' own lack of resources, technical expertise, or motivation to manage activities overseas and ensure compliance. As a result, some organizations have abandoned the idea of outsourcing the development or manufacturing of new, legacy, or generic finished products after several attempts.

Understanding the Process

There is more to marketing pharmaceutical products in the US than just filing an ANDA. In the worst case scenario, some companies hastily decide on a product, produce some data and information, and mail several binders to the FDA. They then wait for the letter to arrive that announces the approval for their submission.

As a submission does not ensure approval, even a successful pre-approval inspection by FDA does not ensure a profitable outcome when it comes to marketing a generic drug. Success requires determining and focusing on the right opportunities, utilizing the right people and tools, and doing the right thing.

For companies in developing countries and for startups or even established firms in the US and Europe, choosing the right generic product to develop and manufacture would determine the future success and sustainability of the company.

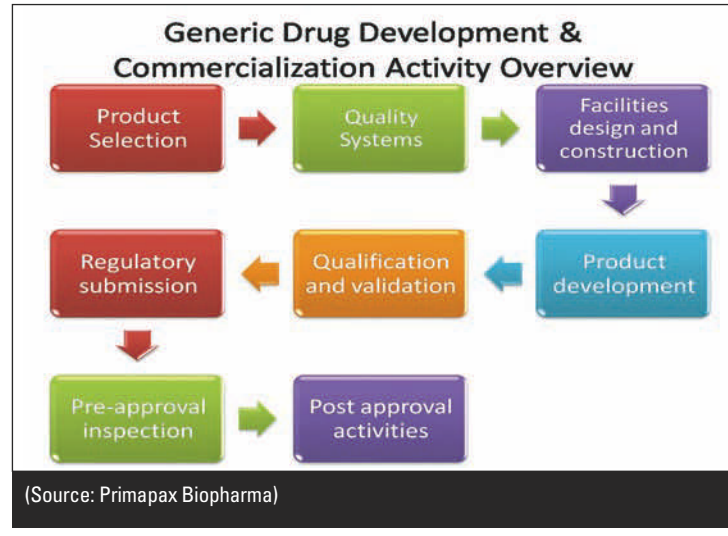
There are examples of organizations that have set up operations in the US or overseas that have

Patent Expiry of Major Drugs

Year	No. of Drugs going out of Patent	Estimated Sales (US $ Billion)
2007	14	20 to 25
2008	10	18 to 22
2009	06	20 to 25
2010	09	10 to 15
2011	10	25 to 30
2012	10	20 to 22

Source: Chemical Weekly (May 2008) & to July 2008

(Source: Chemical Weekly)



(Source: Primapax Biopharma)

begun to develop half a dozen generic drugs in parallel – only to eventually confront technical difficulties with difficult-to-formulate drugs, a lack of sales and customers, or price pressures from competitors – after receiving the necessary regulatory approvals.

When deciding on which generic drugs to develop and market, it is important to ensure that a market analysis is performed, the sales and distribution channels for the specific drug category have been determined, and potential customers have been established. It is critical to complete a thorough technical due diligence of the product to be developed. It is also necessary conduct a realistic gap analysis between the requirements to formulate or manufacture the product versus the company's or contract organization's true technical and manufacturing capabilities.

In addition, it is vital to keep in mind that innovator companies can sometimes utilize different "anti-generic" strategies to keep away potential generic drug manufacturers. These strategies could include:

- The launching of authorized generics
- Creating a secure innovator-buyer relationship before the patents have expired
- Developing a strong portfolio in the product category
- Submitting citizen petitions to the FDA
- "Ever-greening" the drug by modifying the existing product such as launching extended release versions

The generics industry can be profitable if suitable products are chosen to be developed and marketed, the compliance requirements are met, customers are established, and the price is right. Selecting the right generic drug to make and sell, and anticipating the technical, compliance, legal, and regulatory hurdles, is the first and perhaps the most critical step in establishing or maintaining a successful organization.

Quality Emphasis

Quality should be built into the product and testing alone cannot be relied upon to ensure product quality. As the "FDA Guidance for Industry Quality Systems Approach to Pharmaceutical current Good Manufacturing Practices (cGMP) Regulations" indicates, the key concepts that are critical to the pharmaceutical quality system are:

1. Quality
2. Quality by Design and Product Development
3. Quality Risk Management
4. Corrective Action and Preventive Action (CAPA)
5. Change Control
6. The Quality Unit
7. Inspection Model

Unfortunately in many instances, there has been a lack of understanding of what it takes to build a robust quality system within manufacturing and testing organizations both in and outside the US. In some cases, organizations are under the delusion that simply having a large number of Standard Operating Procedures (SOPs) for all the different tasks is sufficient to ensure the quality of products.

In certain facilities, the number of SOPs that are needed to manufacture and support one product exceeds several hundred. This makes it almost impossible to train personnel, manage document control activities, or comply with such a large number of documents in any meaningful fashion.

These organizations have ignored the fact that the purpose

of implementing a quality systems approach is to enable manufacturers to efficiently and effectively validate, perform, and monitor operations, and to ensure that the controls are scientifically sound and appropriate. A quality system is one example where more may not necessarily be better.

For these organizations to be able to ensure product and facility approval by the FDA and a continuous supply of compliant products, quality must be built into every aspect from facility design and construction to equipment selection and qualification, process validation, manufacturing and testing, and all day-to-day operations.

During the past couple of decades, a large portion of US drug manufacturing capabilities have vanished and more pharmaceutical products, which are destined for the US market are being manufactured overseas. In many countries around the world, companies and entrepreneurs are constructing new facilities or are revamping and modifying existing ones to meet US FDA requirements. In many instances, these efforts fall short.

When first embarking on a new pharmaceutical facility, consideration will need to be made as to what cGMP requirements will apply to the project and how they will impact the project lifecycle. These may differ based on many variables but there are common general requirements that cover all the cGMPs worldwide.

Based on an assessment of the regulatory requirements for the type of product and where it will eventually be marketed, the engineering group must first begin to define the GMP requirements for the facility. Generally, issues and areas that are to be considered during the design phase will include:

1. Products, processes, and equipment
2. Location and facility layout including environment and containment strategy
3. Automation and level of technology
4. Equipment selection
5. Material and people flow
6. Regulatory requirements
7. Validation strategy

These basic requirements can then be refined for the various aspects of the project to allow the facility to be engineered properly, adequately, and in a compliant fashion.

Constructing and validating a pharmaceutical facility is a complex task and requires project management skills, technical oversight, and daily attention to details – in order for the company's technical and manufacturing staff to eventually take over a facility that can produce a compliant product at the required volumes.

Many believe that developing a generic drug is simply reviewing the innovator product's label and formulating the generic version using the same Active Pharmaceutical Ingredients (API) and excipients. Unfortunately this is far from reality. Different dosage forms present different challenges both in formulation and process development. Although perhaps the formulation and the scale up of a true solution is in most cases straight forward, scientists and engineers could face difficulties with certain solid dose products, creams and ointments, or suspensions.

Quality by design means developing a product and a manufacturing process that will ensure that the product consistently attains a predefined quality at the end of the manufacturing process. This should be applied from the onset.

In addition, quality by design, in conjunction with a robust quality system, would provide a framework for the transfer of product knowledge and process understanding from drug development to the commercial manufacturing processes.

Validation

As more facilities are built overseas and an increasing number of activities are outsourced, most of the facility and equipment qualification and validation tasks are entrusted to the equipment vendors or third-party contractors. Partly due to repeated layoffs and organizational restructuring, many US companies today do not have the resources to perform these tasks on their own. The same issue and perhaps in a more severe form applies to startup companies.

In most cases, the vendors and independent contractors are experts in what they do and at least in theory can deliver service and compliant qualification and validation documents. However, this can only be achieved if the right vendors are chosen. A comprehensive user requirement document needs to be developed at the beginning of the project and in collaboration with the vendors.

Also, simply relying on the vendors and contractors to perform the qualification and to produce the compliant documents is risky and is in violation of cGMP requirements. Every qualification and validation protocol and report, and every deviation must be reviewed and approved by qualified internal personnel before they are accepted.

In addition, it is important to remember that in accordance with the quality systems approach, validation is not a one-time event, but an activity that must continue throughout the life of a product. Therefore, as experience is gained in commercial production, opportunities for process improvements may become evident. The organization's internal personnel can

eventually capitalize on these opportunities.

Many first time applicants underestimate the time that it takes to prepare and submit a well designed and well executed ANDA. When it comes to generics, a major portion of the regulatory submission is taken up by the Chemistry and Manufacturing Control (CMC) documents. To ensure process efficiency, it is important to first agree upon and develop a list of activities and documents that are needed to be submitted to the FDA and then assign responsibilities and timelines to each task.

Regulatory affairs professionals can usually develop a detailed template of the submission based on FDA expectations beforehand. This will become useful in organizing the documents that need to be filed.

All of the documents that are to be filed must first be re-viewed and approved by appropriate departments – typically product development, technical services, and quality. The worst that could happen to a submission is when incorrect information or failed results are filed. This situation can easily be avoided by a thorough review of documents by trained and experienced personnel before the former are forwarded to regulatory affairs.

It is helpful to be mindful that for most products, the manufacturing of stability batches and the conducting of stability studies are usually the rate limiting step before filing a regulatory submission.

Therefore, in order to shorten the time that is takes to perform all the necessary tasks and at the same time to ensure the quality of the regulatory submission, it would be wise to organize all other tasks around these two activities.

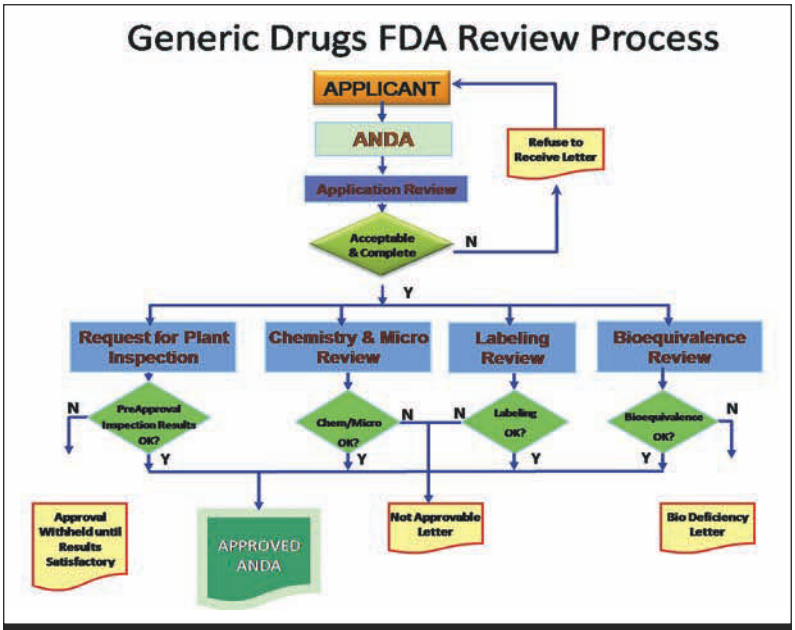
Pre-Approval Inspection

Pre-Approval Inspections (PAI) are a prerequisite to launching an NDA or ANDA product in the US, and are an essential element in the FDA approval process. There are primarily three reasons for FDA's PAI:

1. Verify the manufacturer's compliance with cGMP
2. Verify the accuracy and completeness of the manufacturing related information that has been submitted in the ANDA
3. Evaluate the manufacturing control for the pre-approval batches upon which the ANDA approval is based

Before and during the PAI of a facility, the primary goal of site management should be to manage the inspection effectively. This means to completely understand FDA expectations and to

Drug Manufacturing



(Source: Primapax Biopharma)

communicate them to all personnel, prepare the site, organize and provide the documents and information that are requested as proof of evidence of compliance, and interact appropriately with the inspectors.

The FDA's Drug Manufacturing Inspection Compliance Program, which contains instructions to FDA personnel for conducting inspections, is a systems-based approach to inspection and is consistent with the agency's quality system model. During a PAI, one should expect to be asked questions that are related to any areas that affect the product for which the inspection is taking place.

The FDA inspection team normally includes a lead investigator and depending on the type of product, could comprise of a microbiologist, a chemist, or personnel from any other discipline. Depending on the product category and the inspectors' backgrounds, the areas that are addressed during an inspection could vary to some degree. However, questions regarding the handling of failures and deviations, out of specification results, operator training, facility qualification, material segregation, and vendor audits should always be expected.

Pre-approval inspections are typically challenging. At best, they disrupt daily operations while in the worst case scenario, could result in a loss of revenue and damage the company's reputation. However, one should not be overly concerned if the facility that is to be inspected, has been designed and constructed with cGMP guidelines for the particular product; if the personnel are appropriately trained and the training is fully documented; and if the quality systems are in place.

Post Approval Activities

Upon the completion of a pre-approval inspection and the approval of the ANDA, the generic drug manufacturer can usually start marketing the product in the US. However, manufacturing a pharmaceutical drug is a responsibility that requires constant diligence, communication, and the continuous monitoring of the manufacturing and quality aspects of the drug. In addition, it is necessary to conduct the trending of the data that is obtained from the facility, manufacturing process and customers.

Post drug approval is also an important part of FDA's area of focus. The goal of these activities is to monitor the ongoing safety of marketed drugs. This is accomplished by reassessing drug risks, based on new data that is obtained after the drug has been marketed, and recommending ways of appropriately managing that risk.

A vital part of FDA's mission is to monitor the safety and effectiveness of drugs that are currently available to the American people. To meet this goal, it has in place, post-marketing programs that monitor marketed human medical products for unexpected adverse events. These programs alert the agency to potential threats to public health. Manufacturers of prescription medical products are required by regulation to submit periodic adverse event reports to the FDA.

After a drug is approved and marketed, the FDA uses different mechanisms such as Pharmaceutical Industry Surveillance to ensure that firms adhere to the terms and conditions of approval that have been described in the application, and that the drug is manufactured in a consistent and controlled manner. This is performed by periodic, unannounced inspections of drug production and control facilities by the agency's field investigators and analysts.

Selecting, developing, manufacturing, and marketing generic drugs can be financially rewarding. However, it is also a complex and sometimes expensive process with many pitfalls, if it is not carried out correctly. In every step of the process, beginning from facility design to the manufacturing of every batch upon approval of the ANDA, cGMP requirements for the facility and the quality of the finished product must be adhered to, to ensure the approval and continuous supply of compliant and efficacious drugs. **PA**

A Workflow Approach

Mass Spectrometry and its related technologies offer accuracy and efficiency in the identification and structural elucidation of impurities in a drug substance.

Robert Plumb, senior applications manager;

Michael Jones, senior applications chemist;

Marian Twohig, senior applications chemist;

Karen Haas, senior marketing communications, Waters Corporation

The ability to understand the levels of pharmaceutical impurities in drug manufacturing is not only a regulatory necessity, but a business imperative. However, the analytical determination of impurities is often time-constraining and resource-consuming. It requires a range of mass spectrometry capabilities as well as software to facilitate the data processing of these complex impurity data sets.

A multidisciplinary approach to im-purity analysis was explored using a systematic workflow that is capable of the specific and sensitive detection and determination of impurities that are present in the quetiapine hemifumarate Active Pharmaceutical Ingredient (API) drug substance.

The designed approach incorporated chromatographic resolution, impurity identification, and rapid structural elucidation facilitated by intelligent and user-friendly software. This work flow-based methodology improved the ability to evaluate known and unknown impurities in a pharmaceutical drug substance.

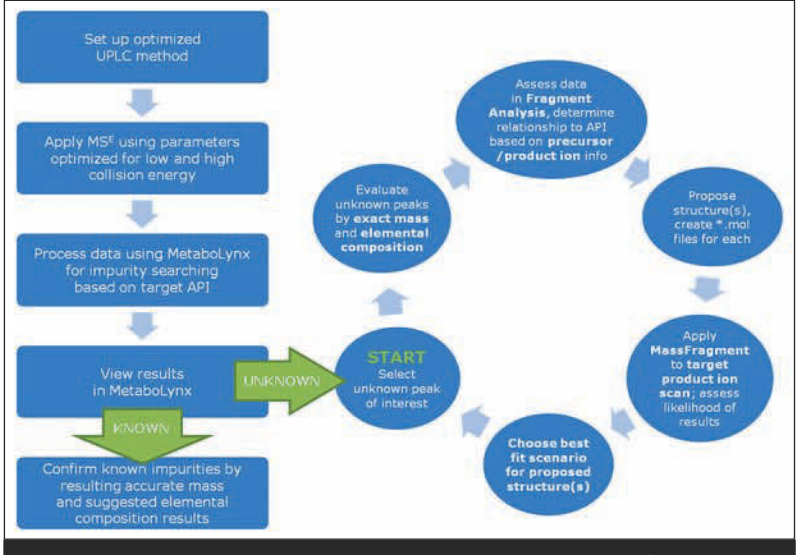


Figure 1: Workflow for impurity identification in an API impurity profile. (Source: Waters Corporation)

Experimental Conditions

The instrument system that was used for this analysis was an Ultra Performance Liquid Chromatography (UPLC) system that was fitted with an a UPLC BEH C_{18} 100 x 2.1 mm, 1.7 µm column. The mass spectrometer was fitted with an Electro-Spray (ES) positive source.

The software processed chromatographic and exact mass data to report retention times, peak area, mass accuracy, and isotope distribution values for m/z found. Elemental compositions were confirmed for known impurities and proposed for unknown impurities. The software also performed a fragment analysis, correlating the precursor ion information of the low-energy-collision Mass Spectrometry (MS) scan to that of the product ion information of the high-energy MS scan.

The high-collision-energy MS scan data was imported into mass fragmenting software, a chemically intelligent structure elucidation tool for the structural assignment of product ions. This is where the structural fragmentation pathways of the impurity compounds were proposed, based on the likelihood of breaking certain bonds.

The workflow approach that is shown in Figure 1 may require several iterations to determine the accurate result for the unknown peak of interest. Evaluation of the data can be more involved depending on the complexity of the compound; however, the general workflow remains constant. The benefit of this approach is that it provides a systematic data-driven association to correlate the variety of data that is acquired by the two scan functions that are generated by MS^E experiments.

The software enables the application of user-defined filters to configure how the reported data is viewed in the browser window. Some useful techniques to apply meaningful data filters

were identified by investigating proper integration parameters. Mass defect filters, the dealkylation tool, spectrum intensity thresholding, and selection of components relative to the compound in the elemental composition tab, all proved useful in displaying more confident data.

For example, to obtain elemental composition for every peak that is found in a chromatogram, the analyst would typically need to combine MS scans and perform background subtraction for each peak of interest and then generate individual elemental composition reports.

To streamline this process, the browser populated all impurity peaks integrated in the Time-of-flight (Tof)-MS ES+ chromatographic trace with associated elemental compositions, mass accuracy, and isotope pattern scoring – and displayed the results in a single window (Figure 2).

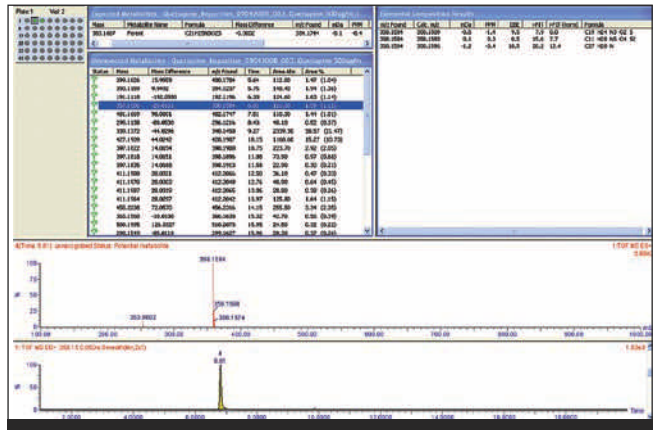


Figure 2: Browser window displaying the various chromatographic and MS spectral information that is generated by the MSE experiments. (Source: Waters Corporation)

Evaluating Impurities

Evaluation of the unknown impurity peaks by exact mass and elemental composition of quetiapine hemifumarate using data acquisition, processing, and interpretation software indicated that the mass accuracy of the API quetiapine was reported to be 0.4 ppm. A total of 80 impurity peaks were listed. Upon adjustments to integration and data filtering, 44 peaks were found to be relevant. Non-relevant peaks were observed to be anomalies of initial integration of noise and peaks with extremely low-level response in UV and MS detection.

Ten known impurities were observed with an average mass accuracy of 1.3 ppm. Two known masses, 398.19xx and 412.20xx, had three and four separate retention times listed respectively. The masses with multiple chromatographic retention times, which indicated possible structural isomers, were [M+H] = 398.19xx and observed four peaks, three of which met the reporting threshold.

The observed [M+H] = 398.1900, 398.1896, 398.1913 at Retention Times (RT) of 10.75 min, 11.08 min, and 11.58 min, with measured mass accuracies of 0.5 ppm, 1.5 ppm, and 2.8 ppm, respectively, resulted in an identified elemental composition of $C_{22}H_{28}N_3O_2S$. Also [M+H] = 412.20xx observed five peaks, four of which met the reporting threshold.

The observed [M+H] = 412.2066, 412.2048, 412.2065, and 412.2059 at RT of 12.50 min, 12.76 min, 13.06 min, and 13.97 min, with measured mass accuracies of 1.7 ppm, 2.7 ppm, 1.5 ppm, and 4.1 ppm, respectively, resulted in an identified elemental composition of $C_{22}H_{28}N_3O_2S$.

In terms of the unknowns that were identified, of 21 entries for 15 chromatographic peaks, peaks identified as doubly charged species were $[M+2H]^{2+}$ = 353.1512, $[M+H]^{+}$ 705.3013 at RT = 17.20 min; $[M+2H]^{2+}$ = 309.1256, $[M+H]^{+}$ 617.2514 at RT = 17.36 min and; $[M+2H]^{2+}$ = 684.2089 with a large fragment at [M+H] = 382.3485.

Peaks with multiple m/z ions; which could be possible coelutions, included; Peak RT = 15.96 min observed [M+H] = 510.2073, 299.1627, 399.2523 (three intense m/z values) and Peak RT = 17.42 min observed [M+H] = 653.3301, 592.1955 (two intense m/z values).

From these, it is possible to generate and assess the data in the fragment analysis function of the data acquisition, processing and interpretation software by determining the relationship to the API based on the MS^E precursor/product ion information.

Fragment Analysis

The fragment analysis tool aligned the high and low collision energy data that were simultaneously collected during the MS^E acquisition. The resulting information was displayed in a collective window where the precursor and the collision-induced product ions were evaluated spectrally and presented chromatographically.

The fragment analysis window allowed for numerous iterations by the analyst to assess common fragment ions between peaks of interest (Figure 3). Commonalities were observed between known impurity structures and fragmentation patterns that aided in proposing the structures of other unknown impurity entities.

An assessment of the common fragment ions of quetiapine identified the major fragment ions to be m/z 279, 253, 221, and 158. Of these, Extracted Ion Current (XIC) of precursor 279 was identified in 22 impurity peaks; XIC of precursor 253 was identified in 25 impurity peaks; XIC of precursor 221 was identified in 23 impurity peaks and; 14 impurity peaks were deemed not to be directly related to the parent.

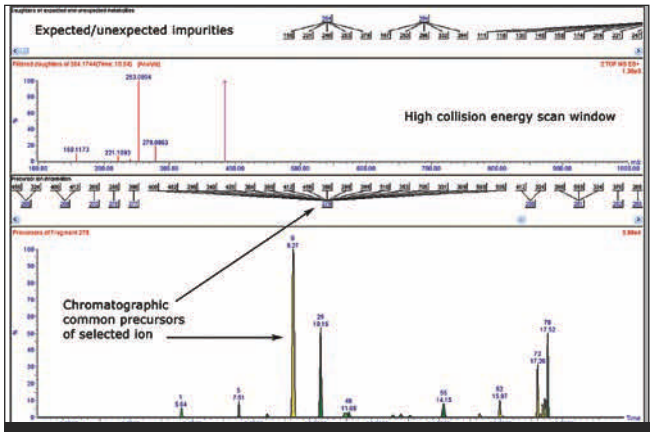


Figure 3: Fragment analysis window correlating the low-collision-energy MS scan data with the high-collision-energy MS scan data. (Source: Waters Corporation)

Structural elucidation was enabled by chemically-intelligent software that combined the aligned high- and low-collision-energy data in the fragment analysis window with the user's input about a hypothesized structure. Before performing the elucidation procedure, a proposed parent structure (or structures) was saved as a "*.mol" file.

Upon opening the software, a dialog window prompted the selection of the *.mol file. The fragment ion information from the fragment analysis product ion's high-collision-energy scan window of the selected observed impurity mass automatically exported to the software tool along with the *.mol file. Potential structures were assigned and scored for the precursor ions in the isotopically-filtered spectrum.

Figure 4 shows an example of the report that was generated by the software for the unknown impurity [M+H] 456.2305. Another conclusion that was determined by the software data was that many of the impurities that were observed in the API quetiapine have the common fragment ions m/z 279, 253, 221, and 158.

Also, the software confirmed similar fragmentation patterns of the imported structures with mass accuracy of generally less than 2.0 mDa. From these data it was also hypothesized that the structure undergoes a structural rearrangement after the cleavage of the piperazine ring. However, this did not seem to affect the mass accuracy of many of the proposed fragmentation pathways of the assumed parent structure of the unknown impurity.

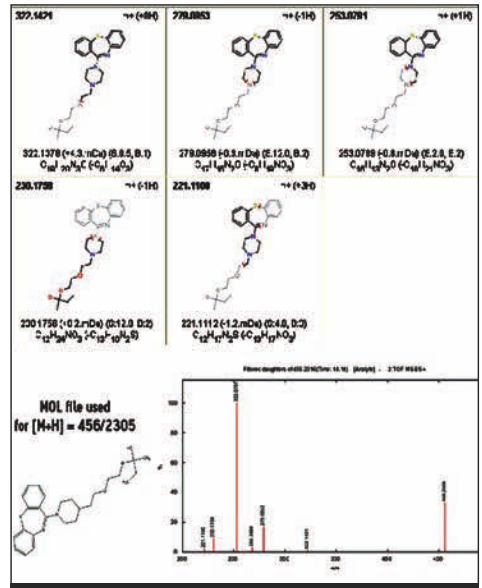


Figure 4: Snapshot of a summary report of possible structures for each of the fragment ions in the isotopically-filtered spectrum. (Source: Waters Corporation)

Information Study

Data collection provided high chromatographic resolution, ample sensitivity, and mass accuracy to identify many of the impurities that were in the quetiapine hemifumarate drug substance. MS^E provided the simultaneous acquisition of both high- and low-collision-energy, maximizing the information that was gathered from a single injection.

This analytical workflow was followed by a deliberate data processing workflow that streamlined the fragment analysis and structural elucidation process and provided greater confidence in the end results.

The browser provided a comprehensive list of elemental compositions for the known and unknown peaks; 10 known impurities were rapidly identified with an average mass accuracy < 3.0 ppm; and [M+H] = 398 and 412 were observed to have a series of structural isomers.

When using mass fragment analysis, a minimum of 25 impurity peaks were identified as being related to quetiapine, utilizing the common fragment ions m/z 279, 253, 221, and 158. And 14 integrated impurity peaks were identified with no common fragment ions.

Finally, the chemically-intelligent software tool enabled the structures of the 10 known impurities to be confirmed. Information of the possible structural isomers for [M+H] = 398 and 412 were easily compared to various proposed structural isomers for best-fit correlation to the high collision energy data.

In some cases where the peak identification was more challenging, the data acquisition, processing and interpretation software was able to help formulate decisions about compound determination.

The combination of these three software tools, along with the optimized instrument configurations for impurity analysis and efficient MS^E acquisition, provided a systematic workflow approach that can readily be applied to identify and confirm known and unknown peaks in an impurity profile.

This workflow-based approach delivered the rapid and systematic set of comprehensive results that were needed to identify and confirm impurities in an API impurity profile. **PA**

Enquiry code: 101E07

Inhaled Drug Delivery: Market Opinion

Drug delivery innovators are designing inhalation devices based on the demands of regulatory authorities and consumers.

Georgina Fradley; Louise Righton; Yuan Lu Ho,
3M Drug Delivery Systems

The market for asthma and Chronic Obstructive Pulmonary Disease (COPD) products is the third largest global pharmaceutical category. Expansion is set to continue, driven by an underlying increase in patients, and the diagnosis and treatment of these medical conditions.

This trend can be observed in Asia, especially in the rapidly growing Chinese market, as patients gain access to a wider range of treatments.

Growing Needs

Asthma and COPD are becoming increasingly prevalent on a global scale. The World Health Organization has predicted that there are 300 million asthma and 230 million COPD sufferers worldwide (many in developing countries). It is now estimated that up to 50 percent of smokers will develop COPD, a figure that is much higher than previous estimates. This, combined with pressures on the cost of health care, has led to an increased focus on the cost of treatment in recent years – driving pharma companies, especially in developing countries, to develop their products in the more cost effective pMDI delivery system.

Inhalation drug delivery has been the mainstay of treatment for respiratory diseases since 1956, which saw the pioneering of the world's first pressurized Metered-Dose Inhalers (pMDI). During the last 50 years, the industry has witnessed improvements to the original pMDI design, as well as the introduction of a range of Dry Powder Inhaler (DPI) devices.

With a plethora of devices that are available through which to deliver New Chemical Entities (NCE) or new presentations of generic drugs – and with the patient becoming increasingly influential in determining which products will be prescribed – a pharmaceutical company's decision criteria must include patient preferences. In addition, regulatory-drivers and cost-drivers remain a focus for developers.

With a plethora of devices that are available through which to deliver New Chemical Entities (NCE) or new presentations of generic drugs, a pharmaceutical company's decision criteria must include patient preferences. (Source: 3M)

Environmentally Friendly Alternative

Another major change for the inhalation market has been the transition away from chlorofluorocarbon (CFC) propellants, in favor of the "ozone friendly" hydrofluoroalkane (HFA) propellants. Whilst many companies have chosen to invest in transitioning pMDI products to the newer HFA propellants, other developers have focused on developing alternative DPI devices. This has led to a change in market dynamics and where pMDIs were once the dominant delivery system in terms of volume and retail sales, DPIs now account for almost half of global sales.

This expansion in the availability of device options has had an impact upon patients: unlike

the pMDI, which is effectively a generic delivery system that can deliver proprietary molecules and/or formulations, each DPI device is unique. Different DPIs use different actuation and aerolization mechanisms, which in turn influence dose delivery.

This means that there is no "one device fits all" solution for DPIs and therefore it is not yet believed to be possible to develop a generic product using a DPI. This poses a problem in the US because CFC-containing albuterol inhalers have been banned from January 1, 2009 as a result of the Montreal Protocol.

Patient opinion has become increasingly important in pharmaceutical device development. (Source: 3M)

Patients have had to get used to the different sensation with the use of HFA-containing pMDIs. Because there is also no generic asthma/COPD product that has been approved by the US Food and Drug Administration (FDA), patients and insurers are forced to pay higher prices for their medication. The race is on to develop generic HFA-containing albuterol pMDIs for the US market, opening up opportunities for pharma companies worldwide. Europe and the US are not the only markets with a current cost focus. With the increases in rates of occurrence and diagnosis of asthma and COPD in the major Asian markets – evidenced by growth in the sales of such products in China and India – many companies are looking to utilize existing technologies to enter these markets.

Market Segmentation

In developing countries, it is likely that two market segments will co-exist: the first consists of branded, differentiated products with a "device-edge" which appeal to affluent, urban-dwelling patients, and command a premium-price; the second consists of generic products in simple delivery devices, such as the pMDI, which offer a low-cost route to market.

The latter devices are familiar to regulators – facilitating the product registration process; and also to patients, thereby not requiring extensive education before use. In addition, technologies offering single dose administration in a low cost disposable device, such as the Conix DPI, could have utility.

However not all changes are focused on reducing costs. The FDA has introduced guidance requiring all new pMDIs being submitted for registration to incorporate a dose counter. A dose counter is a safety mechanism that informs patients as to the number of doses of medication they have left, and to help them to determine when to replace the inhaler.

Before the introduction of dose counters, patients used various techniques to determine when they needed to order a repeat prescription, such as floating their inhaler in water or shaking it to gauge the amount of drug remaining. As these techniques are subjective, it is likely that many patients have been using their inhaler past the number of prescribed doses, thereby exposing them to the risk of sub-optimal dose medication. Research with patients has shown that the introduction of dose counters (mandated in the US and encouraged in Europe) can provide a sense of security, enabling the former to monitor remaining doses in their inhaler more accurately.

Patient Involvement

The patient's opinion has become increasingly important in pharmaceutical device development, and developers acknowledge that the patient's interface with the device is crucial. Evolution in inhaler design will be driven by more informed consumers, confident to demand products to meet their needs and fit their lifestyles. Patients currently demand a list of attributes including: discretion in use; small enough to fit in the purse or pocket; ease of use; organic-feel to mouthpiece; legible and accurate dose counter; looks like a consumer product rather than a medical product.

In the current economic climate, especially in the pharmaceutical industry where pipelines have been shrinking and products are taking more time and investment to commercialize, a convincing business case must be made for developing devices. Whilst the inhaler is a complex device with small changes requiring significant investments, patient preferences have come to the fore in the design and development of improved devices today.

Drug delivery innovators believe that pharmaceutical products, although heavily regulated, should not be any less consumer-researched and design-optimized than other products. Achieving a "device-edge" is possible and worthwhile in this large and competitive market.

The vision must be to make asthma and COPD patients' lives better, bringing devices to give them more confidence and control over their conditions and minimizing the negative effects on their quality of life.

Clinicians have highlighted patient non-compliance as a major cause of poor disease control for many years. A lack of motivation, confusion over the different types of inhalers prescribed, or simple forgetfulness are some of the main reasons for the non-compliance. The pharmaceutical industry has responded by developing combination products such as Seretide (GlaxoSmith-

Kline, UK) , Symbicort (AstraZeneca, UK) and Foster (Chiesi, Italy) which incorporate inhaled corticosteroids with long-acting beta-agonists to provide patient-convenience and ease of use. These products have been successful in recent years.

Other pharmaceutical companies have moved towards "one puff once a day" products – for example the inhaled corticosteroid ciclesonide, marketed as Alvesco (Nycomed, Switzerland) – as a way of improving compliance. Innovations in drug delivery technologies such as the Face Seal Valve will make more "one-shot" products possible in the future and will allow the reformulation of existing brand leaders into more convenient dosage regimes.

Design Considerations

Inhaler design is also a factor which influences patient compliance. The historical issue for pMDIs was the difficulty that patients have had in coordinating breath inspiration with the timing of the press-and-breathe valve mechanism, which releases the drug dose. A solution to this problem was provided through the introduction of the Autohaler breath-actuated inhaler, which uses the patient's inspiratory breath to trigger the valve to release the drug dose. Similarly, DPIs rely on patients to activate the release of the dose through inspiration, some of which are passive and rely on the patient inspiratory rate (which has implications of its own), and others include active mechanisms to provide energy for aerosolization. Patients can also have difficulty in understanding how to operate multiple devices.

These problems have resulted in efforts to resolve the common issues that patients tend to experience when using inhalers. It has also prompted developers to consider the opinions of the patient during the design and development of new devices. Ease of use has become a critical requirement, particularly for DPIs, where the variety of options available means that prescribers and patients must intuitively understand the steps that are required to use a device correctly.

Patient research projects have shown that "feeling secure" is a critical emotion for patients, given the potentially life-threatening nature of respiratory disease and the fact that it can be a frightening and debilitating disease state. Therefore, familiarity of the device is a key attribute. Other features can also enhance the feeling of security: confidence in the number of doses remaining in the inhaler and feedback that the dose has been taken correctly.

The FDA has introduced guidance requiring all new pMDIs being submitted for registration to incorporate a dose counter. (Source: 3M)

In the case of pMDIs, feedback is an inherent feature (because of the taste and the sensation of the plume passing through the mouth and throat). Many patients have also identified feedback that the dose has been taken, as a primary need when using DPI products. This can be addressed in two ways: either through the incorporation of a simple audible click which occurs when the dose is released; or in the case of more advanced devices such as the Taper DPI, a visual "ready" indicator that is used to show patients that the dose has been inhaled.

Issues in Design

Research with specialist asthma nurses, points device developers toward a similar direction: a discreet device that is well designed so as not to look too "medical" will facilitate compliance; and feedback to the patient or carer that the dose has been taken correctly, results in a feeling of confidence in disease management.

The nurses also stress the importance of simplicity in device usage – minimizing the number of steps and making them as intuitive as possible. This helps to instill patient confidence to use the device correctly while assisting in compliance. In the case of particular patient groups such as children or the elderly, the need for these design factors is magnified.

The worldwide market for asthma and COPD products is vast. It is growing rapidly, especially in Asia. In the process of designing products to meet the needs of health professionals and regulators, developers are increasingly focusing on patient needs when developing new and improved devices.

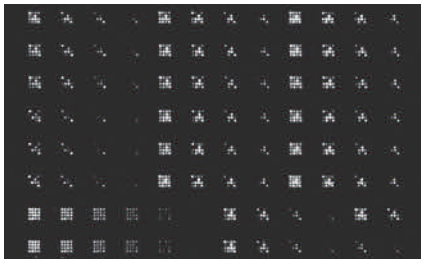
In addition, cost will continue to be a major driver of device design as the Asian market in particular develops into two sub-markets: a market for low-priced, tried-and-trusted pMDI devices to deliver generic drugs to the less wealthy patients; and innovative drug products with a "device-edge" which can command a premium price in the more affluent patient population.

For both patient segments, ease of use, discretion, a non-medical appearance and a feeling of security are key design attributes. Both the established pMDIs and the innovative DPIs are being designed and redesigned to meet these patient needs. **PA**

Enquiry code: 101E08

Product Focus
Lab Equipment

PBL InterferonSource Introduces Multiplex ELISA Arrays



PBL InterferonSource introduces the Quansys Q-Plex Cytokine Multiplex Enzyme-Linked Immunosorbent Assay (ELISA) arrays – high-throughput interferon detection kits that can save time and provide key information for drug discovery and clinical research efforts in the treatment of infectious diseases and autoimmunity.

The kits combine various cytokine antibodies within multiplex arrays to give researchers a better understanding of the simultaneous relationship between multiple cytokines. Examination of these relationships reveals information that can help predict clinical outcomes based on several cytokine and growth factor biomarkers including:

- Assessment of cytokine profiles at various points throughout the course of disease;
- Correlation of cytokine profile alterations with patient responses to therapies;
- Determination of drugs' off-target effects.

The quantitative ELISA-based tests contain up to 16 distinct capture antibodies in each well of a 96-well plate. Each spot is well defined and represents a distinct antibody population. Up to 84 different samples can be assayed for all 16 unique cytokines in less than 2.5 hours.

PBL InterferonSource, www.interferonsource.com

Enquiry code: 101P01

KD Scientific Offers Programmable Syringe Pumps

The Legato 200 series of syringe pumps from KD Scientific offers ease of use through the high-resolution color touch screen user interface. The screen interface enables the user to quickly create configurations and recall them for easy use. The intuitive run screen combines multiple parameters simultaneously with internationally recognized graphic icons.

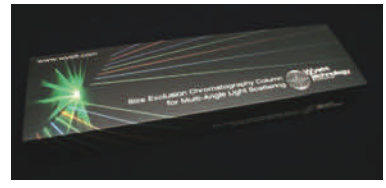
Three basic models are available: Infuse only, Infuse and Withdraw and Push Pull. Each of these pumps is available in a programmable version. Each of the basic models works with one syringe or two and can be reconfigured in the field to be used with multiple syringes. In limited laboratory spaces, the Legato 200 series can be placed on its side to reduce the footprint by four times.

KD Scientific, www.kdscientific.com

Enquiry code: 101P02

Wyatt Technology Launches Size Exclusion Chromatography Columns

Wyatt Technology Corporation has announced the launch of its Size Exclusion Chromatography (SEC) columns for protein analysis by Multi-Angle Light Scattering (MALS). The combined SEC-MALS method has various applications, including quantification of protein aggregation, determination of protein conjugate stoichiometry and confirmation of the oligomeric state of a protein.



The columns cease shedding particles after a short time and produce low light scattering baseline noise and pressure shock resistance.

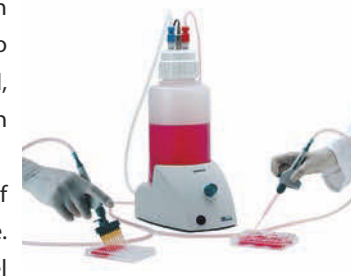
This feature not only ensures high data quality and accuracy, but also improves productivity because less time is required for the columns to "quiet down". Quality consistency is ensured as each column is individually tested using a MALS detector before being shipped.

Wyatt, www.wyatt.com

Enquiry code: 101P03

Integra: Safe Vacuum Disposal of Liquids

Integra has extended its Vacusafe aspiration system with models for laboratories that need to utilize an existing supply of vacuum. The model, without an integrated vacuum pump, has been priced to be affordable by laboratories.



The compact system makes the aspiration of hazardous liquids safe, user-friendly and flexible. The Vacusafe has safety features like the liquid level sensor and the two hydrophobic filters that block potentially dangerous aerosols. A handle makes the carrying and emptying of the waste bottle easier than before. With a range of adapters, the removal of liquids is possible from virtually any container.

Integra, www.integra-biosciences.com

Enquiry code: 101P04

Calendar of Events

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 11-12, 2010
World CRO Summit
Shanghai, China
http://worldcrosummit.tpgi.org/

Mar 16-19, 2010
World Pharma Trials Asia 2010
Singapore
www.terrapinn.com/2010/pharmatrials/

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

Mar 16-19, 2010
Pharma R&D Partnering World Asia 2010
Singapore
www.terrapinn.com/2010/rnd/

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

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

Mar 24-26, 2010
BIT Life Sciences' Annual World Congress of Vaccine
Beijing, China
http://www.bitlifesciences.com/wcv2010/default.asp

Mar 30-31, 2010
Healthcare in Asia 2010 – Investing in tomorrow
Singapore
www.economistconferences.com/health2010

Apr 14-16, 2010
LabIndonesia
Jakarta, Indonesia
http://www.labasia.com/index.php?option=com_content&view=article&id=53&Itemid=53

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
CphI 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/

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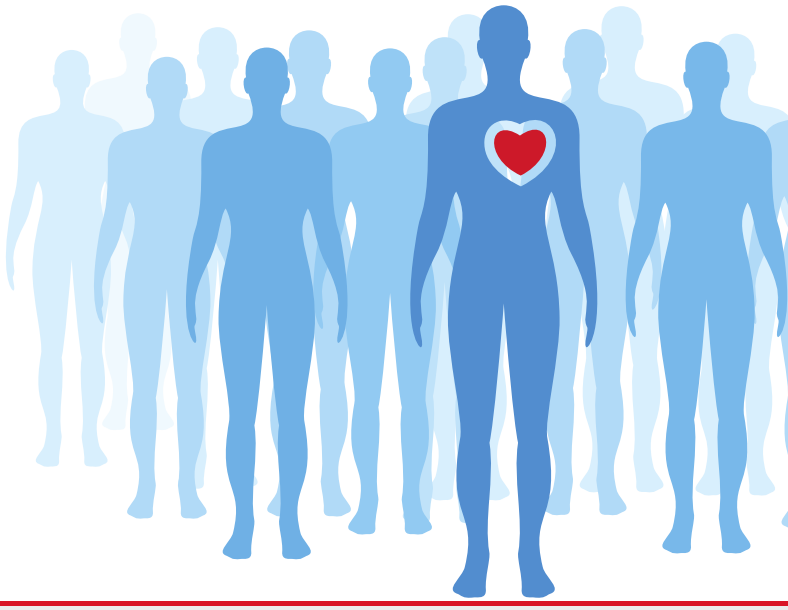
AD INDEX

Healthcare in Asia 2010

March 30th – 31st, 2010
The Fullerton Hotel, Singapore



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For more information about registration or sponsorship opportunities, please contact Sally Au at:

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A number of the region's health ministers, top practitioners and industry thought leaders have confirmed their participation and will speak at the roundtable:

Mr Khaw Boon Wan
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Ms Jae-Hee Jeon
Minister for Health, Welfare and Family Affairs, Republic of Korea

Dr Endang Rahayu Sedyaningsih
Minister of Health, Republic of Indonesia

Dr Chih-Liang Yaung
Minister, Department of Health, Taiwan

Dr York Chow
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Mr Shane Solomon
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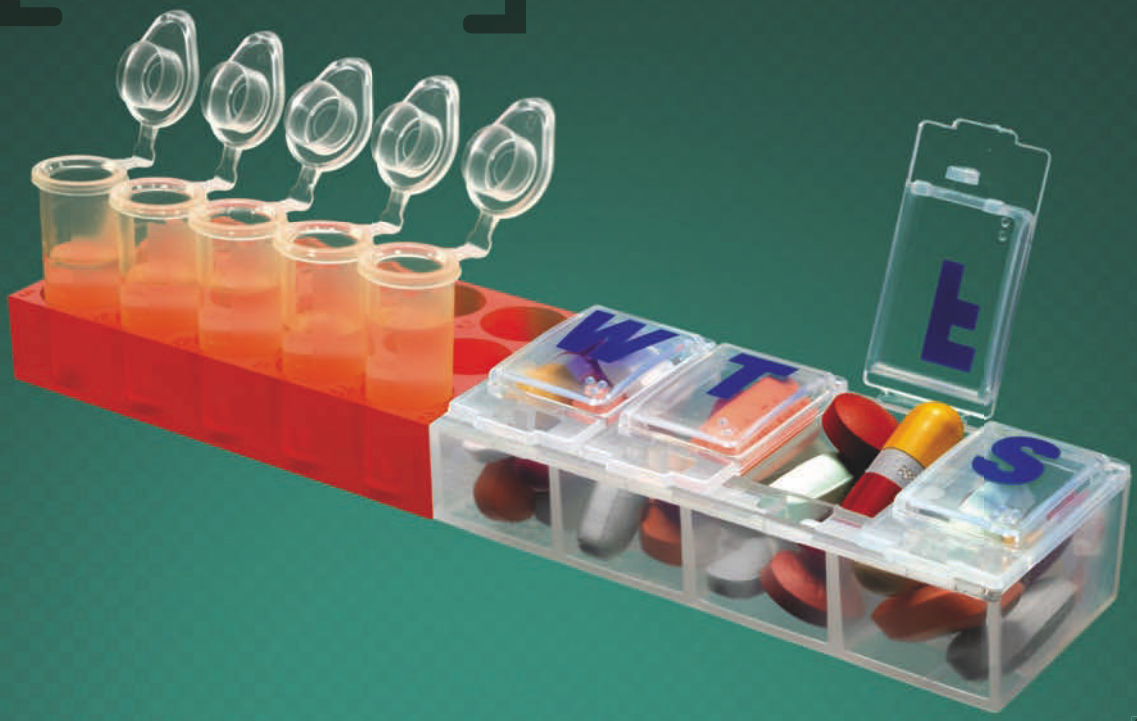

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