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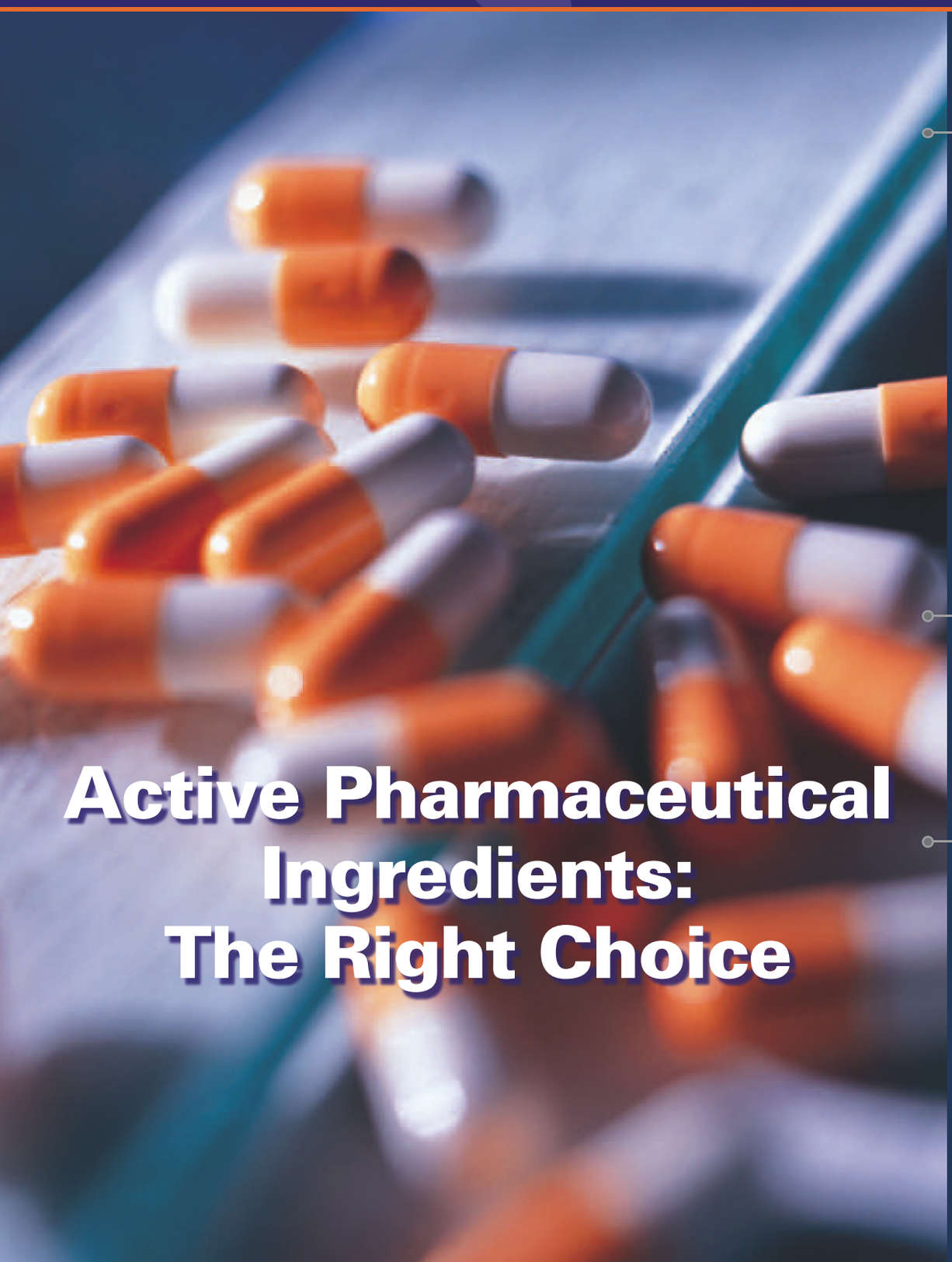

Active Pharmaceutical Ingredients: The Right Choice

Drug Manufacturing

Understanding Process Analytical Technology (PAT) in Pharma Manufacturing

PAT: Measuring Return on Investment

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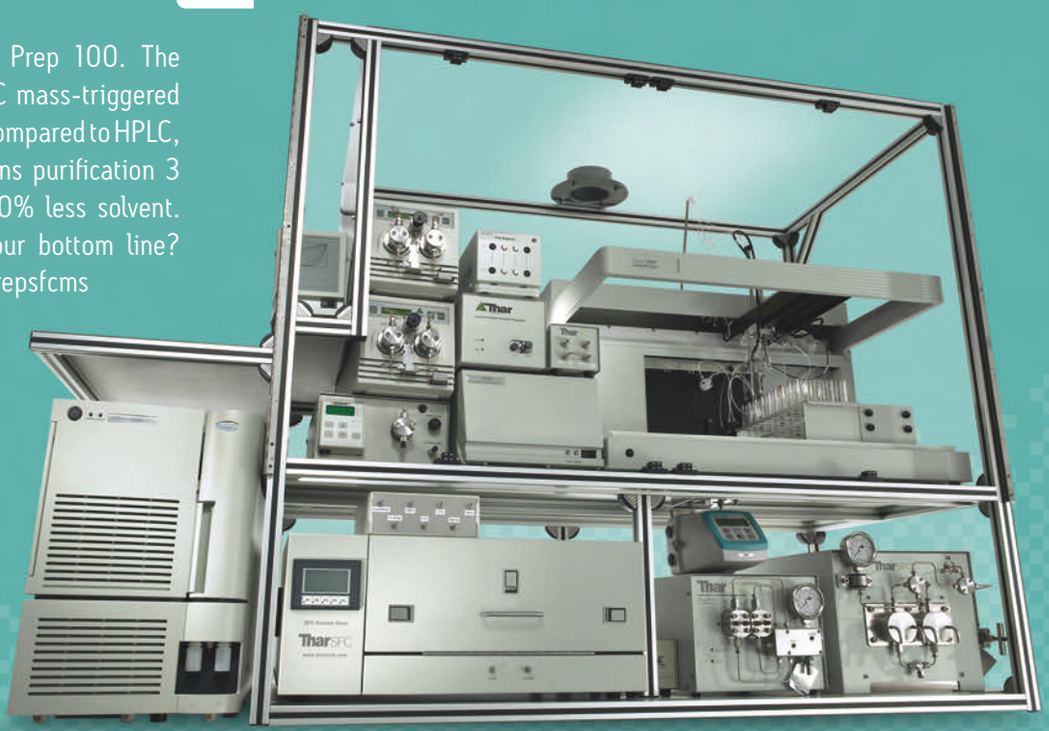

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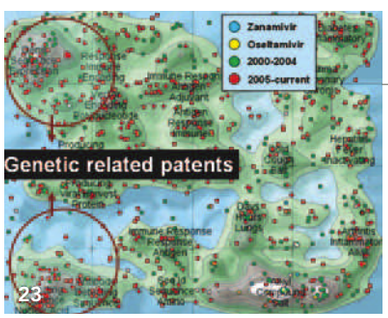

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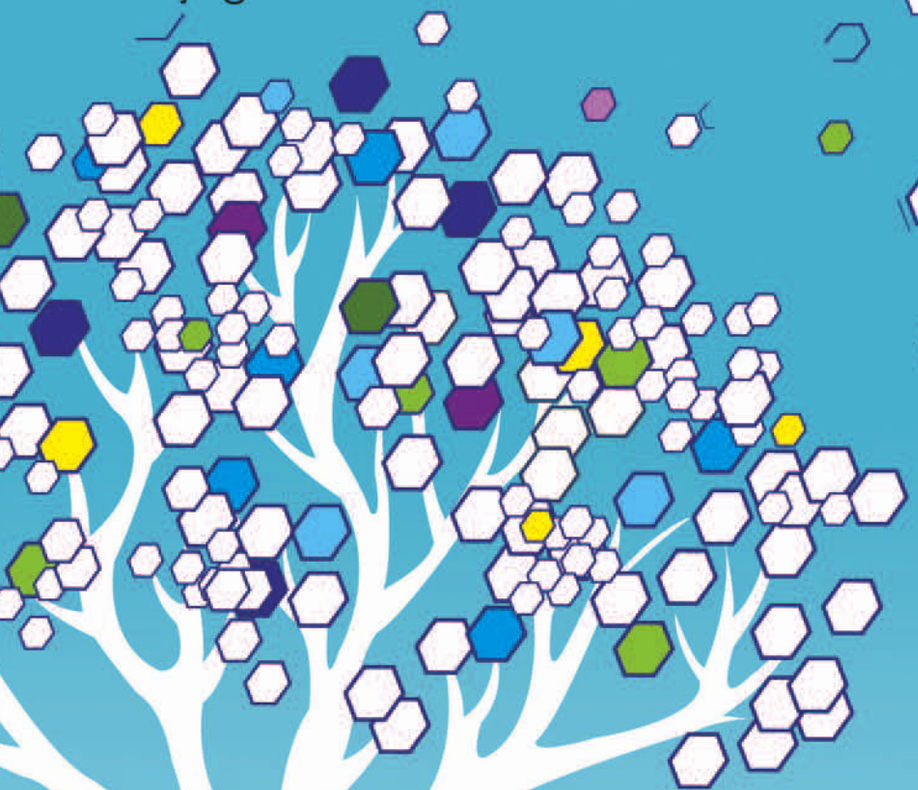

Sino-India Partnership Program & India Buyer Port (IBP)

SIPP SINO-INDIA PARTNERSHIP PROGRAM

SIPP & IBP program was successfully launched at API China & INTERPHEX China Spring 2009 event in Xi'an. During the program, India's top pharmaceutical manufacturers and API traders marked their presence to source for the best Chinese suppliers at the event.

This special program will be part of the Autumn 2009 event in Beijing.

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Editor's Note

Michael Tham
Editor

Poles Apart

The element of risk is part and parcel of most business activities. Managing it is a necessity that requires skills in its identification and assessment.

In pharma manufacturing, companies are increasingly turning to lower-cost Active Pharmaceutical Ingredient (API) producers in the East – even though the differences in production expectations between the two parties could pose unforeseen hazards.

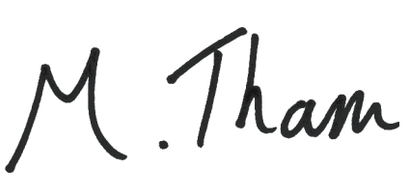
In a bid to reduce cost structures while ensuring consumer safety, companies have to take steps to ensure that these sources of API operate in compliance to international quality and safety standards. However, changes often do not occur overnight. As advised by Ariba, a provider of on-demand spend management solutions, patience is the key in integrating low-cost suppliers into pharma supply chains.

Elsewhere in Asia, developments are taking place that seek to overcome differences in language. Thermo Fisher Scientific has launched a series of free on-demand webinars for the laboratory informatics community in China and Australia. The program is delivered in both Mandarin and English, offering the pharma industry in each country the same benefits.

Despite the inherent challenges that are present in diversity, there are also benefits that can be realized. Indeed, companies that recognize the advantages of leveraging on each other's strengths, have come together to achieve a common goal.

AstraZeneca and Nektar Therapeutics have entered into an exclusive license agreement for two drug development programs relating to the treatment of pain and constipation. Similarly, Amylin Pharmaceuticals and Biocon have agreed to jointly develop, commercialize and manufacture a peptide therapeutic for the treatment of diabetes.

With strengthening relationships between the East and West and increasing collaborative efforts among pharma companies – staying on top of the game will require greater mastery in the art of understanding and managing diversity. **PA**



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Ariba: Ensuring Quality in API Supply

With expiring patents and growing gaps in revenue a reality in the global pharmaceutical industry, an increasing number of drug manufacturers are beginning to evaluate their supply chains to identify opportunities for savings, so that they can continue to bring products to market and remain competitive.

With greater frequency, pharmaceutical firms are seeking sources that can deliver key inputs such as Active Pharmaceutical Ingredients (APIs) at a lower total cost than their current suppliers. And in many cases, they are looking abroad. While there are gains to be had from sourcing in low-cost countries, there is also substantial risk.

As part of its Category Chatter series, Ariba has created a podcast that is aimed at helping companies to understand these risks and develop strategies. This is to enable them to reap the cost-saving benefits of sourcing in emerging nations without sacrificing the quality of their products.

"As the costs of healthcare continue to soar, pharmaceutical companies are taking aggressive steps to revamp their cost structures," said Christopher Merchant, director, Healthcare Sector, Ariba Spend Management Services. "But they face a unique challenge in that while seeking ways in which they can generate savings, they must also identify and resolve any areas in the supply chain that might present risk, as the consequences of contaminated products can have a dramatic effect on the global population."

To help do this, Ariba has compiled a list of steps that pharmas can take to enforce their quality standards when sourcing APIs abroad:

1. Do not let the government do the work for you

Pharmaceuticals should always hold its API sources to a higher standard than those set by the US Food and Drug Administration (FDA). As stringent as FDA directives may be, approvals can be attributed to political and other factors that may prevent proper scrutiny and exposure of substandard operations.

2. Invest in building a strong on-the-ground presence

It can take a pharmaceutical company several years to identify API sources in low-cost nations and get them operating smoothly and in compliance with quality standards. Consequently, a serious commitment must be made upfront, to build a strong on-the-ground presence to manage the process.

Walking suppliers through processes and procedures a few times or conducting random site visits is not enough. Suppliers must be monitored thoroughly and regularly to ensure that they do not cut corners or misinterpret expectations.

3. Limit the number of offshore partnerships

Every year, new API sources sprout up in low-cost countries, covering a variety of specialty chemicals. This presents an opportunity to diversify the supply chain and maximize cost savings by partnering with a number of suppliers.

However, given the time and financial commitment that is involved in developing each API source, it is wiser to emphasize quality over quantity. Instead of trying to cultivate the same high standards within many suppliers and risking a weak link, concentrate on one or two key suppliers to ensure quality and safety over the long haul.

4. Emphasize safety in supplier selection

One of the best ways to create and enforce high standards is through a rigorous and thorough process to identify the right suppliers. One way to do this is to make safety a key criterion for selection in the initial Request for Proposal. This not only makes suppliers aware of safety at the onset, but also sets a baseline that can be used to measure performance on an ongoing basis.

5. Be patient

Companies that have successfully integrated low-cost country suppliers into their supply chains did not do so overnight. Pharmas must give themselves adequate time to build supplier networks that take into account their unique needs, challenges and risks.

"Successful offshoring will be a key driver of success for drug companies in the long term," Merchant said. "Pharma companies that invest in solutions and processes now that enable them to evaluate and manage new markets and sources of supply, will realize the greatest benefits that low-cost regions can generate down the road." **PA**

Ambry Genetics Attains Agilent's Certified Service Provider Status

Ambry Genetics has announced that it has completed certification to become a service provider on the Agilent microarray platform. The initial certification is for Comparative Genomic Hybridization (aCGH) which is an application that is used by researchers to discover and detect genomic copy number variations within specific genomes.

The Certified Service Provider program comprises a select list of strategic organizations that pass a rigorous assessment to use the latter's microarray platform. The program combines the provider's focused expertise with the complete microarray workflow to create specialized services or complete genomic research solutions. **PA**

Vetter Opens Facility in the US

Vetter, a provider of aseptically pre-filled injection systems, will open its Vetter Development Service (VDS), a customer service facility located in Chicago, US. The company can now process and test small quantities of materials by bringing the development process closer to key customers, enabling greater cooperation at the earliest stages of development. The approximately 25,000 sq ft facility will open at the end of 2009. **PA**

GKLog Celebrates 21st Anniversary

Griffin Kinetic, a member of GKLog Holdings, celebrated its 21st anniversary in September. The occasion also served to launch its new brand identity as GKLog.

The company has moved into specialized logistics services for the pharmaceutical and biotech sectors. It views this as a natural progression from its niche marine business. Leveraging on its Good Transportation Practice (GTP), GK has embarked on a mission to train its staff to handle temperature sensitive, high value products and hazardous substances. It aims to support pharmaceutical companies based in Singapore.

Ted Tan, deputy chief executive of Spring Singapore, was the guest of honor for the brand launch event. "The logistics industry is a critical industry to the Singapore economy. As a sector on its own, the logistics industry comprises of approximately 9,200 enterprises, employing over 180,000 workers and contributed to 9.4 percent of Singapore's GDP in 2007. The sector is also an important enabler that strengthens Singapore's position as a manufacturing and distribution hub." **PA**

Lonza Celebrates Groundbreaking of Facility in Singapore

Lonza Group has celebrated the groundbreaking of its facility for cell therapy. The facility is located at the Tuas Biomedical Park in Singapore and adjacent to the company's large-scale mammalian manufacturing facility.

The event was officiated by S Iswaran, senior minister of state for Trade & Industry and Education.

In his welcome address to celebrate the groundbreaking ceremony, Stefan Borgas, CEO of Lonza, said, "Cell therapy is expected to be one of the most important innovation drivers of modern medicine and this facility reinforces Lonza's position as a custom manufacturer of cellular therapeutics."

Construction of the facility will begin early in 2010 and it is expected to begin manufacturing therapies within the first two suites by mid-2011. The facility is designed to accommodate additional suites that can be built to meet incremental customer demand. The total investment for the first phase will be approximately CHF 30 million (US$29 million). **PA**

Proteomics International: Predictive High-Throughput Peptide Drug Discovery

Proteomics International has achieved a 67 percent efficiency in its drug discovery process, using an alternative approach. The proof of concept has been confirmed with results coming from the external verification of its data.

"We can offer a more efficient use of resources", says Dr Richard Lipscombe, Proteomics International's MD. "The advances in biological technologies and computing power have opened doors for the pharmaceutical industry. We have created a generation of tools for drug discovery, and have applied them to one of nature's oldest chemical cocktails – venom."

In the company's proprietary process, *Bioven*, a venom is fully sequenced to produce a database of peptides. Each molecule is then analyzed by computer to predict its function. For any chosen activity the best candidates are selected and synthesized. It requires venom from only one bite or sting, and the database can be easily rescreened any time, for any desired function. Due to their origins, these molecules have the added advantage of proven solubility and stability.

Working with peptides isolated from Australian arthropods, the team targeted two bioactivities to validate their process – pain relief and bactericidal. After promising early results from antibacterial screens, the company selected a group of six molecules that it predicted would be ion channel blockers, and four were significant positives when tested in an animal model – a 67 percent hit rate.

Dr Scott Bringans, Proteomics International's Research Manager, said, "We predicted analgesic and antibacterial peptides and found them at 100 times the industry normal success rate. But that is not the end of the story – we can go back to the library and pull out other classes – protease inhibitors, neurotoxinsvthe possibilities are vast. We have barely scratched the surface".

The company has a secure source of new venoms under an agreement with the Northern Territory (Australia) government and the company collects scorpions, spiders and centipedes using a team of expert collectors based in Alice Springs.

The company will be seeking expressions of interest from potential industry partners to take its Bioven discovery process to the next level. **PA**

Cover Story

API: The Right Choice

What drug manufacturers need to know, when selecting an Active Pharmaceutical Ingredient (API) supplier

Peter Werth,
CEO, ChemWerth

The US Food and Drug Administration (FDA) is ramping up regulatory efforts with funding and reform. Generic drugs are becoming increasingly visible because of their importance in healthcare. How do companies keep up with FDA regulations and ensure that Abbreviated New Drug Applications (ANDAs) get approved?

Cost Control

In the current politico economic climate, prescription medication is especially important to consumers who can save 50 percent or more in drug costs if a generic version of a brand name drug is available to them. Considering that generics account for nearly 70 percent of prescribed medications, and consumption is likely to increase because of its lower cost, it is no surprise that many governments are tightening their regulatory oversight of drug manufacturers.

There is a direct correlation between the percentage of the world population using a product and the amount of regulatory oversight that comes with it. Widespread use of a product necessitates current Good Manufacturing Practices (cGMP) compliance, and careful quality control, especially when a product is developed using ingredients from a number of diverse sources.

The global regulatory landscape has permanently changed since the Heparin fiasco, and drug manufacturers need to be vigilant about cGMP compliance and quality control. This is because the US FDA is increasing its vigilance and scrutiny of drug manufacturing operations in response to mounting evidence of gaping holes in regulatory oversight.

There appears to be a gap between what the FDA deems acceptable in generic drugs and what consumers are now beginning to see as acceptable. Recent articles in mainstream US publications such as *Self Magazine* and the *Wall Street Journal* outline the concerns that consumers have had with generic prescriptions, where minute differences have led to major consequences.

In 2006, one patient's 300mg prescription for the antidepressant Bupropion XL, a generic version of Wellbutrin XL, caused side effects. The drug notably worsened depression and various gastrointestinal problems before it was discovered in 2008 that the 300mg pill approval was based on an extrapolation of studies performed solely on the 150mg pill.

This example was reported as recently as June this year. It implies that there are still regulatory gaps that need to be addressed. However, it is apparent that recent legislation has enabled the FDA to begin increasing its ability for regulatory oversight, as evidenced by the openings of FDA bureaus in India, China, Europe, and Central America, with plans to expand to Mexico, South America, and the Middle East. The FDA Globalization Act of 2009, sponsored by Rep John Dingell (Michigan) should be able to provide opportunities for greater reform.

Considering that generics account for nearly 70 percent of prescribed medications, and consumption is likely to increase because of its lower cost, it is no surprise that many governments are tightening their regulatory oversight of drug manufacturers.

Approaching the Problem

Only four percent of all ANDAs are approved by the FDA in their first go-round. Most of the 96 percent of the unapproved ANDAs fail because of a lack of chemistry documentation

related to the Drug Master File (DMF). Considering that it takes an average of 18 to 24 months from submission to approval, it is imperative for drug manufacturers to have reference to a DMF that will be acceptable within one or two review cycles. It can be challenging to perform the necessary research that is needed to stay up-to-date with the FDA's increasingly stringent requirements.

The main difficulty with "meeting" FDA requirements is that, in many cases, it is very much like trying to hit a moving target, which incidentally, is an effective way to move the drug industry steadily towards better drug safety and efficacy.

The main source of the aforementioned lack of chemistry documentation, formally known on paper as "chemistry deficiencies," has been found to be closely associated with the drug manufacturers' source of Active Pharmaceutical Ingredients (API). Some of the more obvious reasons for chemistry deficiencies in ANDAs include:

- Lack of transparency in the manufacturing process to be able to certify that no process patents are infringed;
- Slow response times;
- Not setting proper quality specifications;
- Lacking in an understanding of how to respond to the FDA;
- Changes in manufacturing process;
- Unsecured and unqualified raw material supply chains;
- Non-disclosure of solvents;
- Not identifying toxic impurities.

The API and its source is heavily scrutinized by the FDA because the former is key to a drug's efficacy and in many cases, its overall safety. ANDA submissions can be complex in that there are usually ingredients from multiple entities/sources in a single drug. If one of those entities lacks sufficient documentation, especially the API source, the drug will likely be rejected and the ANDA unapproved.

Therefore, the key to ANDA approval is to assure that the API is developed meticulously, and that all of the development and manufacturing procedures strictly adhere to established cGMP compliance and quality standards. This is so that all documentation is available to the FDA and to other governing bodies when required.

This is a large and time-consuming task for any drug manufacturer. Most API manufacturers are not located near the drug manufacturer's site. This makes it almost impossible to assure cGMP compliance without working through an agent/broker that has qualified regulatory personnel and offices located in the same country as the API manufacturer.

Drug manufacturers need to be vigilant about cGMP compliance and quality control. (Source: ChemWerth)

Choosing an API Source

So what are the options for sourcing an API? To begin with, there are certain factors that should be considered, including the geographic market breakdown of generic API sources. China, India, and Italy currently account for the majority of generic API manufacturers serving the world's estimated US$17 billion market. China produces about 70 percent of the world's generic API, India manufactures about 19 percent, and Italy accounts for about nine percent.

Apart from geography, the criteria for choosing an API source should include:

- A predictable response time;
- Chemistry and manufacturing expertise;

- Reliable quality;
- Compliance assurance;
- Regulatory expertise,
- Intellectual property security;
- Security of supply;
- Language.

Predictable response time is important when responding to an FDA deficiency, in view of the time sensitive aspects of ANDA approvals. Compliance assurance and regulatory expertise are key because they demonstrate one's ability to navigate current FDA policy and one's overall knowledge of the approval process.

API manufacturers generally are not trained to respond accurately and quickly to DMF deficiencies. Intellectual property security and trade secrets are a major issue for most manufacturers. It is difficult for manufacturers to fully disclose their manufacturing processes even in a DMF.

But above all, an API source's track record is the litmus test for trust because a reputable establishment should routinely exceed the quality standards set forth by the FDA, which makes sense financially, ethically and morally. If a drug is manufactured to the highest of universal quality and safety standards, it will likely be safe and effective and is more likely to be approved in its first FDA review cycle.

After establishing the above parameters, there are a number of options available when selecting an API supplier, based on its type of business model that is best suited for one's company goals. A general rule is that the cost to develop and file a DMF costs approximately US$250,000. This cost applies, no matter which option is used.

The first option is to manufacture the API in-house – ie, vertical integration. This option is ideal if resources are available for a completely self-reliant business model where API production is possible, as well as having the necessary equipment and staff in place. It is advantageous to be in full control, with the benefits of lower fixed costs, Intellectual Property (IP) confidentiality, and secure supply chains and logistics.

However, the cost of infrastructure is high and if any capabilities are limited, or problems arise, there is no support. If the infrastructure does not exist or requires extensive renovation or modification to support API manufacture, the amount of time that is required to do so at this stage may jeopardize the entire program.

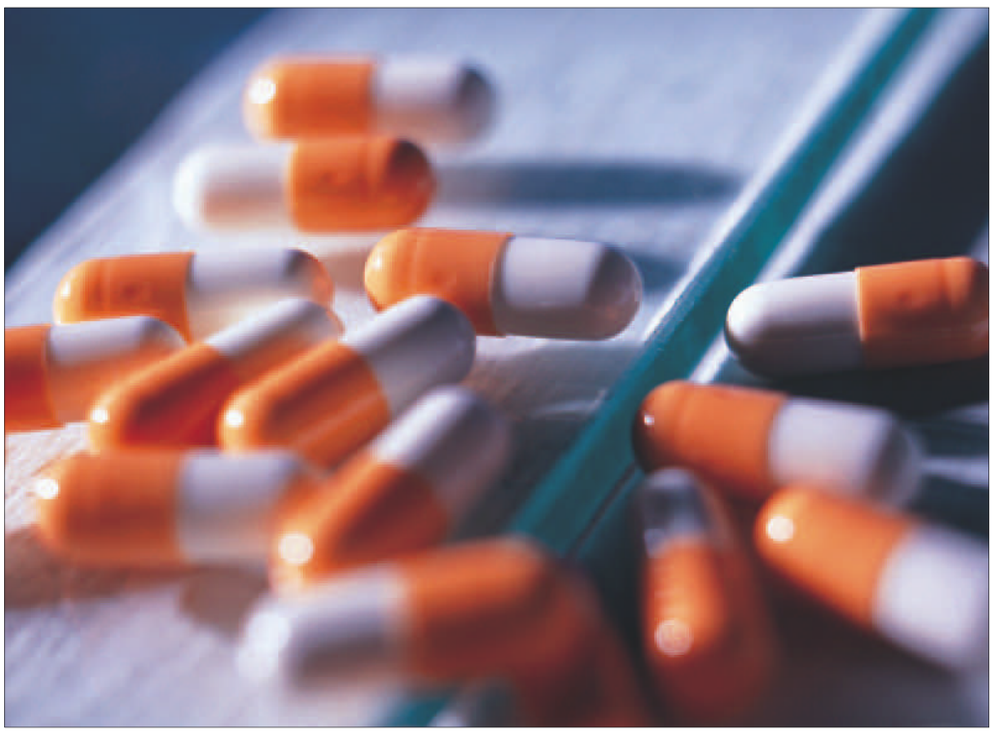
Another option would be to look for a lower cost manufacturer to be the API supplier. Even with this arrangement, it will still cost US$250,000 per DMF API. Eventually these costs need to be absorbed even if they do not show up in the API. This option is more risky because the quality and safety of the API can be called into question.

Response time can be unpredictable, the quality of the production facilities may be questionable, supply chains and logistics are not secure – issues that can affect the ANDA approval process. In addition, IP confidentiality may not be guaranteed.

Competitive Collaboration

A third option would be to work with a competitor to develop the API. While this is usually a last resort, there may be rare situations where it is the only option available. Here, supply and logistics security and availability may be suitable for both parties, but costs could fluctuate depending on the mutually agreed business plan.

There are obvious competitive conflicts in terms of transparency and confidentiality,



Only four percent of all ANDAs are approved by the FDA in their first go-round. Most of the 96 percent of the unapproved ANDAs fail because of a lack of chemistry documentation related to the Drug Master File (DMF).

especially in regards to each party's facilities and processes. Another potential pitfall can be the long-term security of supply; will the newfound "frenemy" adopt one's goals in their own business plan?

If going with the lowest bidder sounds too risky and going to a competitor is out of the question, another option would be to build a partnership with a company that has expertise in developing and getting APIs FDA approved, in order to develop the drug together. In this way, risk and responsibility are shared, but so is the reward.

A full service product development company with an excellent track record is an ideal partner because there is an assurance that the processes used are free of process patents, and that the quality will meet the FDA and ICH guidelines for quality. The API manufacturer will have to be FDA approved. Although the API may come at a slightly higher cost, the necessary documentation of the quality and processes that are involved in making the drug are available. The information is well organized for the partner and more importantly, for the FDA.

With a reputable full service provider, the quality materials are guaranteed to be used in all processes, along with strict self-screening procedures that go over and beyond normal quality control practices that are performed at the lower cost manufacturers' facilities. Supply chains are secured, IP remains confidential, and response time is quick. The fast response time is attributed to a full service provider's knowledge base and familiarity with the approval process and current FDA policy.

The dosage form manufacturers' ANDA approvals will come in 9-12 months for most products, because of the full staff support capabilities that provide all required paperwork and support. These support capabilities are especially invaluable when there is any last minute issue or follow-up work that is required for approval.

The reason for a full service provider to consistently aim to exceed FDA standards is simple: It makes sense to do everything possible to ensure that a drug is approved, for both financial and ethical reasons. If a drug is manufactured with the health of the patient in mind, the drug is more likely to be manufactured with the best intentions and in the finest conditions possible. **PA**

Enquiry code: 097E01

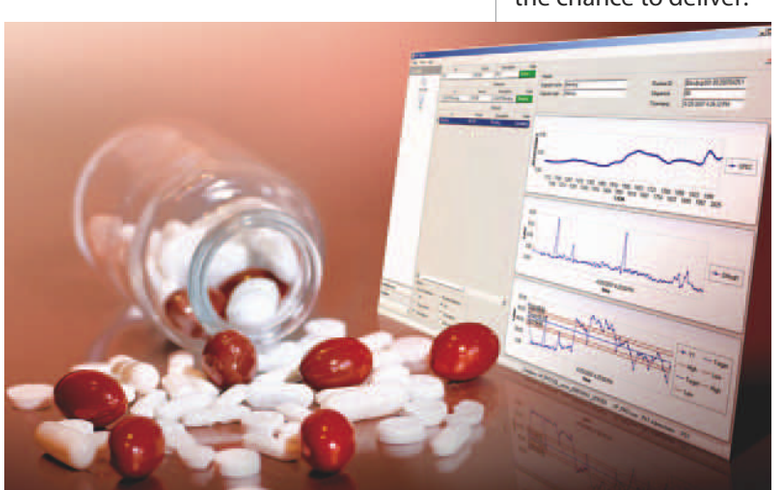
Process Analytical Technology (PAT): Measuring Return on Investment

Companies need to consider both short and long-term needs in order to maximize the benefits from PAT implementation.

Eugene Yeo,
director,
Pharmaceutical Industry Southeast Asia,
Siemens

Process Analytical Technology has the potential to dramatically change pharmaceutical manufacturing. But how can companies judge the Return On Investment (ROI) case for PAT? Despite its advantages, many companies remain hesitant about its implementation. The benefits are great but the investment cost is potentially high.

By offering companies the chance to understand and control their processes, both at the R&D and manufacturing stages, PAT enables continuous quality verification and with it, the chance to deliver:



(Source: Siemens)

- Consistent quality;
- Lower costs;
- Speed up product development and release;
- Improve market responsiveness;
- Reduce supply chain bottlenecks.

Companies will also be rewarded by a lighter regulatory touch if they can gain PAT-led control of the product design space.

Nonetheless, pharmaceutical manufacturers face a complex and, in some respects, contradictory set of demands. On the one hand they have the opportunity to make significant investments in automation and process technology but on the other hand, they face cost pressures, meaning that such investments must deliver maximum benefits.

Manufacturers face a future drug market that may be more personalized, posing key dilemmas on whether the manufacturing plant development should be on a large or small scale.

Short and Long Term Returns

An article by Johnson and co-authors investigated Multi-Variant Data Analysis (MVDA) applications in the biotech industry. There are four application areas that are typical for PAT in general where MVDA is combined with Design Of Experiment (DOE), and have added value to pharmaceutical production. They are:

- Optimization of large-scale production;
- Establishment of process comparability and trouble-shooting;
- Routine monitoring of manufacturing processes;
- Raw material characterization and screening.

These areas highlight the extent to which companies can start with a small application of PAT on one part of the production process, for example, on a single unit operation such as drying, before moving on to a more global view. A typical starting point, for example, could be the establishment of an end-point detection mechanism for a dryer or granulator.

Some of the most common applications of PAT relate to the on-line monitoring of blending, drying and granulation steps.

In this way, companies are able to deploy PAT to resolve already identified problems in their current manufacturing processes. This identification of clear, current improvement goals is the first of two important yardsticks for the ROI evaluation of PAT.

The second yardstick needs to be a look at the bigger picture – where the company wants its manufacturing to be in the future. Therefore, besides identifying the current manufacturing problems that require improvement, companies should develop a clear manufacturing vision and involve all parts of the business in looking ahead on a 10-15 year time frame.

The approach outlined in the case illustration allows companies to prioritize specific problems within the context of long-term change. The range of specific concerns could include a need to fix or improve existing processes, speed up new product development, reduce site to site transfer risk and times, reduce validation costs or improve quality reliability. Most companies are likely to want to realize a blend of these benefits.

Their immediate priorities will be determined by the current state of play of their manufacturing and its fit with their regulatory, market and business goals. More importantly, they need to combine this review of current wider concerns with the type of longer-term scenario planning outlined in the case illustration. Figure 1 outlines the steps that companies might take to put this process into practice.

Figure 2 provides an overview of the type of overall decision-making process that a company needs to undertake. The current manufacturing infrastructure has to be assessed in the light of the future manufacturing vision (in line with the global company's objectives). What are the current bottlenecks and the possibilities for improvement?

The resulting list of improvement proposals have to be evaluated, to judge what they bring to the company and whether they help to achieve the manufacturing vision and its objectives. Depending on which market the company is in, the regulatory constraints need to be superimposed to make sure that there are no unpleasant surprises. Even for those countries that are actively driving changes (such as the US FDA), it is important to involve the regulators early on in the process.

Four Change Scenarios

The outcome of this type of process will be a view about what type of manufacturing strategy and plant the company needs in the medium to long-term timeframe (5-10 years). The answer may be different from plant to plant and many companies are likely to need to plan for a mix of scenarios.

For example, a company may choose to implement relatively modest improvement investments in a plant to manufacture a product that is nearing the end of its patent period (scenario one in Figure 3).

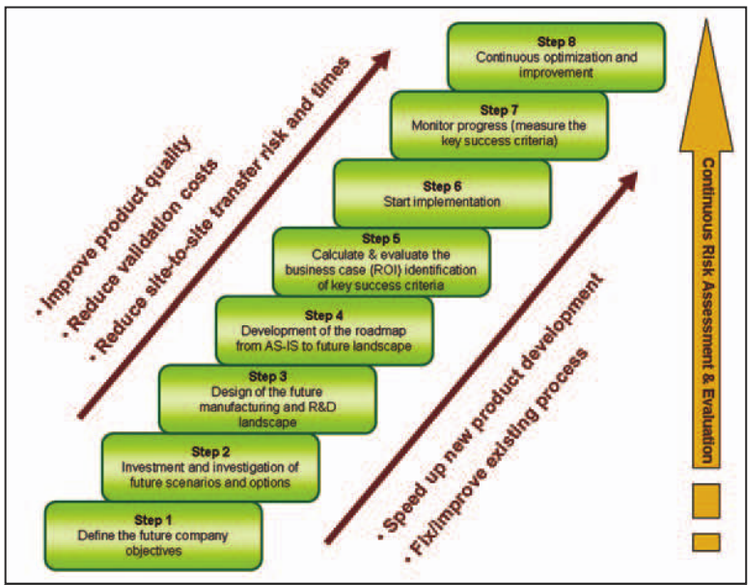


Figure 1: Moving towards the manufacturing vision (Source: Siemens)

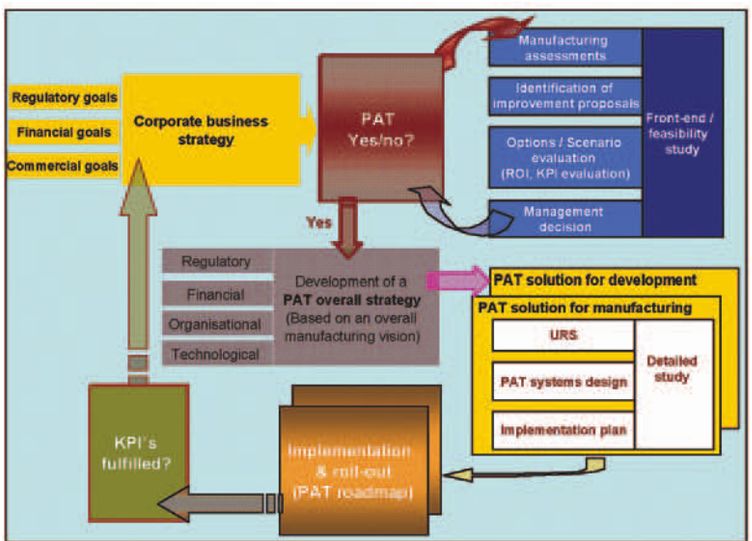


Figure 2: The pharma manufacturing change context (Source: Siemens)

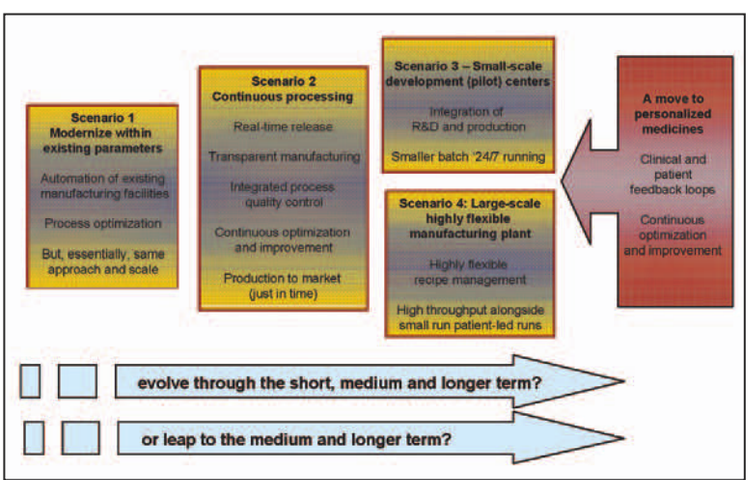


Figure 3: Four Change Scenarios (Source: Siemens)

Case Illustration: Manufacturing Vision Development

A pharmaceutical company has a product that will soon run out of patent and generic manufacturers are becoming strong competitors. Reducing manufacturing costs has been defined by this pharmaceutical company as a key business objective.

Typical Response

The company decides to appoint a team of experts whose task is to review manufacturing and propose optimization proposals. After a couple of months this team presents the cost reduction initiatives to their management. A list of suggestions have been made, such as better planning to remove Work-In-Progress (WIP) and to lower inventory; optimization of manufacturing yields and costs by enlarging the batch size (higher filling levels in manufacturing equipment); in-line inspection instead of manual inspection; installation of process analyzers to detect batch end-points, for example for drying and blending, The team shows that these measures will deliver a reduction in manufacturing costs.

A 'Manufacturing Vision' Response

Another company takes a different approach. Instead of appointing a team to look for optimizations and improvements, it first organizes a high level meeting with representatives from various departments – R&D, manufacturing, sales and marketing, regulatory affairs. The aim of the meeting is to investigate what the needs will be in 5-10 years, taking account of business challenges, technological options and regulatory opportunities.

The group has already looked at their current product portfolio and future portfolio, based on their pipeline. It has investigated the consequences of this new portfolio on the current manufacturing infrastructure. It has considered what the future manufacturing landscape will look like in order to be able to cope, not just with the new product portfolio, but also with the future market and environmental requirements, business model requirements, regulatory changes etc.

A scenario planning exercise has supported the exploration of possibilities and future scenarios. This study results in the identification of a manufacturing vision, which describes the required future manufacturing landscape that will best fit with the most likely scenarios.

This vision makes it easier to identify the gaps between the current "as is" manufacturing situation and the future "to be" one. It also helps to indicate the improvements and changes that the company can already start to implement. A roadmap linking the "as is" and the future "to be" situation enables the company to focus on the improvement and optimization projects that help it move to the future situation.

The company can avoid investments which, taken in isolation, might have a sufficient ROI to implement, but when looked at in a fuller context, would not achieve a more sustainable advancement for the company. This broader perspective enables the company to move forward in the knowledge that it is not just investing in little islands of optimizations but is linking them to a bigger quantum leap forward.

Elsewhere, it may choose to plan for a rapid and full-scale move to PAT, enabling the full realization of the US FDA's vision of real-time product control and release, based on continuous manufacturing operations (scenario 2 in Figure 3).

Companies will also need to be mindful that a possible trend towards personalized medicines will increase manufacturing complexity and, in turn, pose challenges for Manufacturing Execution Systems (MES) and quality systems. A larger variety of products and a variation of the same products will require greater flexibility in production as well as closer integration along the whole pharmaceutical chain – R&D, manufacturing, sales and the end customer.

Scenarios three and four in Figure 3 highlight how companies will face a choice between big plants with flexible recipe production, versus small-scale development (pilot) plants which will also be production facilities with dedicated lines.

For both models of production, industrial Information Technology (IT) systems will play a strategic role. This requires flexibility in the first model to support the flexibility of production that will be necessary and, in the second smaller scale model, to link production with continuous development and learning from clinical trials.

The regulatory stance will be a key factor in this mix and at present, regulators are investigating how to support this evolution with the appropriate regulations and guidelines.

A key influence will be on the demand side and it is likely to see a mix of large scale, high throughput facilities, handling generic production and micro-process centers, concentrating on higher end personalized medicines. Pharmaceutical companies therefore need to investigate the investment in planning for a potentially different manufacturing future as well as responding to pressures on their current manufacturing set-up.

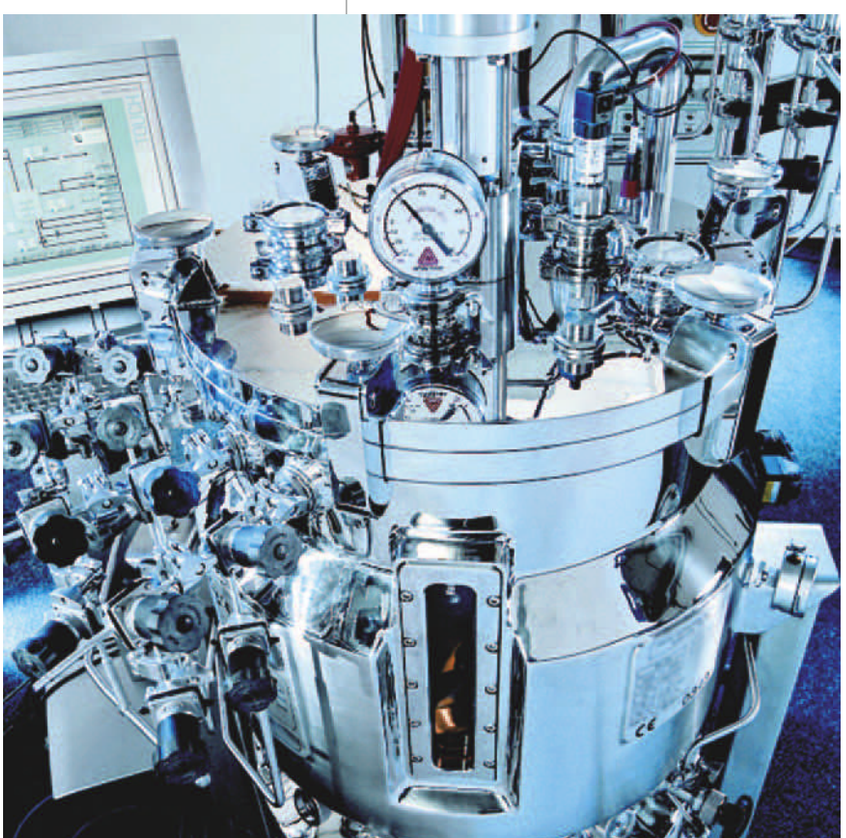
Manufacturing Infrastructure

Once they have chosen between the different possible manufacturing visions and have completed some scenario planning, companies will need to decide on the manufacturing and IT infrastructure that will be required for the chosen scenario. One inhibiting factor has been the absence of software that enables the full integration of PAT tools and all information flows during the processing and online comparison of process data with previous or historical data.

A PAT project at the Process Development Laboratory of the Netherlands Vaccine Institute (NVI) was used to develop software that would fill this gap. The software, known as SIPAT, has helped to develop a real-time process verification tool for all critical process attributes of the cultivation process step of the Bordetella pertussis bacteria, used for whooping cough vaccine.

The goal of the project was to develop an alternative process development methodology and advanced process monitoring and control techniques that could lead to the real-time release of the end product without final quality testing.

The software enables the collection of data and the full integration of all information flows during processing and online prediction calculations as well as the comparison of the actual batch trajectory with the "golden batch" trajectory. With SIPAT, the institute can integrate lab models with sophisticated near-infrared and mass spectroscopy measurements and data gathered by sampling, to build a full process model.



The incorporation of PAT is expected to enable the rapid migration of development of pipeline processes into large scale manufacturing. (Source: Siemens)

Wider Implementation

This technology is being used to develop the process on a two-liter research-scale bioreactor. The knowledge gained will facilitate an up scaling of the process to commercial manufacturing. There are plans to implement PAT both in other cultivation processes and in other unit operations, such as freeze-drying or process chromatography.

The software has now been developed for wider pharmaceutical R&D and manufacturing applications. It gives pharmaceutical companies a common system architecture. It serves as a common user-friendly interface for all PAT tools (process analyzers, multivariate statistical tools, LIMS, MES, process control, historian) and can be fully integrated into the manufacturing and development architecture.

The incorporation of PAT is expected to enable the rapid migration of development of pipeline processes into large scale manufacturing.

Companies can frame a ROI case for PAT implementation on a range of scenarios, ranging from future development and manufacturing facilities, to the fixing of specific snags in current manufacturing processes, such as end-point detection for a dryer or granulator. An effective ROI framework needs to combine a review of both immediate, short-term improvement issues with longer-term scenario planning that is built around a future manufacturing vision. Companies that succeed in bringing together a holistic view of the short- and long-term are more likely to make PAT implementation decisions that deliver a more effective ROI. **PA**

Enquiry code: 097E02

Understanding Process Analytical Technology (PAT) in Pharma Manufacturing

The effective implementation of PAT involves in-depth process analysis and in certain cases, changes in organizational structure.

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Wee Chew,
senior research fellow,
Process Science and Modelling, ICES,
Agency for Science,
Technology and Research

Process Analytical Technology (PAT) is becoming increasingly important in pharmaceuticals manufacturing. As regulatory authorities continue to push for greater certainty in process outcomes and higher levels of product quality, the demand for PAT looks set for further growth.

PAT is often understood as the deployment of advanced measurement techniques during processing. However, the name is potentially misleading; it would be a mistake to think of PAT as simply being technologies for process measurements.

Understanding Technology

As defined by the US Food and Drug Administration (FDA), it is "a system for designing, analyzing, and controlling manufacturing through timely measurements (ie, during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality".

This definition implies that PAT is a much more complex concept. It is necessary to define the Critical Quality Attributes (CQAs are those attributes of the product that have an impact on the patient), to identify how they can be measured and to know what actions to take, on variations in those measurements.

None of these are easy. PAT has to be based on a sufficiently sound understanding of the process and sources of variation; otherwise there is a risk that measurements will be misinterpreted, or be insufficient to ensure quality outcomes.

The effective implementation of PAT can be challenging as it may well require organizational change for successful delivery. The technology should be considered from the early stages of process development, ideally using the same measurement techniques in the laboratory to investigate the process, as they will finally be used on the plant for monitoring and control.

The key is to identify those techniques that "bound" the process – covering all of the CQAs – with suitable sensitivity to identify significant deviations. It is also important at these stages to have sufficient process understanding to know that there is a low risk of "unanticipated" variability outside PAT detection capabilities.

The four main PAT tools that are suggested in the FDA Guidance are as follows:

1. Multivariate tools for design, data acquisition and analysis;
2. Process analyzers;
3. Process control tools;
4. Continuous improvement and knowledge management tools.

The first two proposed tools introduce a multi-variable or multi-dimensional paradigm

to the analytical instrumentation and data analyses of pharmaceutical processing. Modern process analyzers that provide molecular spectroscopic information such as near- and mid-infrared, and Raman have been extensively reported in the literature to be well developed and suited for PAT implementations in both primary and secondary manufacturing scenarios.

Ensuring Quality

More advanced instrumentation include chemical imaging spectrometers for the near- and mid-infrared and Raman, which provide both spatially and spectroscopically resolved information, according to Gendrin, 2008. Near infrared spectroscopy has been used in both qualitative and quantitative analyses for an assortment of applications such as the:

- Quality control of starting materials, tablets;
- Determination of polymorphs, moisture;
- Active Pharmaceutical Ingredient (API) content;
- On-line monitoring and control of secondary processes like powder blending, granulation, drying, polymorph crystallinity, coating;
- Tablet packaging.

The number of applications for mid-infrared is fewer, ranging from monitoring reactions, pharmaceutical crystallization and polymorphic transformations to pharmaceutical formulation and drug dissolution studies. Raman spectroscopy has been used in both on- and at-line purposes for monitoring reactions, polymorphic transformations, crystallization, and formulation studies.

The intention of deploying process analyzers is to obtain rich process data from on-, in- and at-line implementations, so as to acquire a deeper process understanding for each unit operation. Such understanding is usually obtained not from the direct readings of process spectroscopic measurements but through suitable multivariate statistical analysis or modeling.

This is for two reasons: Firstly, the inherently multivariable and voluminous nature of such data; and secondly, the intrinsic complexity of the chemical processes that these data encode. The discipline of chemometrics is often associated with the elucidation of pertinent (ie, critical) underlying chemical information from process spectroscopic data.

PAT has to be based on a sufficiently sound understanding of the process and sources of variation. (Source: Mettler Toledo)

The suite of computational techniques under chemometrics covers a broad scope:

- Signal preprocessing;
- Principal Component Analysis (PCA) and factor analysis based algorithms;
- Spectral curve resolution techniques (eg, MCR, SIMPLISMA, BTEM);
- Multivariate calibration and regression analyses (eg, PLS, MLR);
- Quantitative Structure-Activity Relationship methods (QSAR);
- Discrimination and classification algorithms (eg, hierarchical cluster analysis, SVM, ANN).

The choice of specific chemometrics methods for analyzing process spectroscopic data largely depends on first, the type of data (eg, reflectance, absorbance, infrared, Raman, UV, etc) and second, on the goal of each analysis, ie, the final set of chemical information desired.

Efficacious process control under the FDA PAT framework involves interfacing between process monitoring (through the first two tools) and control strategies (through control

algorithms) in order to ensure product quality assurance. Also, both the design of product and process development have a strong bearing on the determination and control of critical quality attributes.

Process Control

It has been recommended that appropriate process measurements and sampling, together with rigorous statistical principles, should be used for end point acceptance criteria definition, which can be realized in real-time through Multivariate Statistical Process Control (MSPC).

It is also crucial that analytical instrumental bias, and long- and short-term variabilities are controlled via monitoring measurements against some checking standard. This is to ascertain the robustness of the process measurements methodologies over time.

The fourth PAT tool, ie, continuous improvement and knowledge management, necessitate the collection and analysis of historic process data. Time series analysis, design of experiments and factorial approaches can be applied for extricating process knowledge and understanding over the life cycle of the product and within pharmaceutical manufacturing campaigns.

It is necessary to define the Critical Quality Attributes (CQAs are those attributes of the product that have an impact on the patient), to identify how they can be measured and to know what actions to take, on variations in those measurements.

The realization of PAT tools in pharmaceutical manufacturing is at present, some distance away from full maturity. One vital point to note is the intrinsic multi-disciplinary nature of the work that is involved to successfully implement PAT methodologies.

As such, not only does the PAT development team need to comprise people with specific expertise (eg, process development and analytical chemists, chemical and control engineers, chemometricians, etc), more importantly, team members must be open to learn each others' technical languages and thinking styles so as to harness the necessary synergy for the tasks involved. Often, organizations are not structured to be able to bring these various skill sets together simultaneously and may well require organizational changes to produce good results.

Considerations in Design

The multivariate paradigm in both data analyses and statistical control strategies also poses a challenge in terms of both the learning curve and the implementation in plant situations. Experience has to be garnered for selecting the appropriate process analytical techniques for the desired physicochemical transformation within process engineering design constraints.

It is also imperative to take note of pitfalls whilst choosing chemometrics methods for PAT applications. It is the responsibility of the PAT team to validate and demonstrate robustness in the chosen methods as there are no standardized modus operandi that are universally accepted or approved, as described by Doherty and Lange, 2006.

Furthermore, the four suggested PAT tools are in themselves distinct domains, which require cross-disciplinary interfacing and integration. This is to achieve the intended enhancement of the understanding and control of the pharmaceutical manufacturing process that is delineated in the FDA PAT Guidance.

The implications to pharmaceutical companies in Asia are twofold. Firstly, companies will need to ensure that they have the appropriate skill sets to be able to deliver PAT solutions. For companies that are primarily manufacturers, this may involve increasing skills in process analysis and understanding in addition to instrumentation. Secondly, there is a need to look critically at the organizational structure and to judge whether changes are required for the effective deployment of PAT. The components for PAT are increasingly available, but effective outcomes rely on deploying the right skills at the right time. **PA**

Taiwan Pharmaceuticals Industry: The Need for Expansion

Catering largely to domestic needs, local companies have to take steps to penetrate overseas markets for further growth.

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Manager,
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Ministry of Economic Affairs, Taiwan

Taiwan's pharmaceutical sector is divided into three sub-sectors: Active Pharmaceutical Ingredients (API), western medicine, and botanical drugs. Western medicine includes small molecule drugs that are made from chemical synthesis as well as biologics, or biopharmaceuticals, such as vaccines and antibodies. Botanical drugs are derived from Traditional Chinese Medicine (TCM), an area where the Taiwanese government is aggressively supporting its R&D and application.

The Asian pharmaceuticals industry is playing an increasingly important role in the world. Taiwan is located at the transportation hub of the Asia Pacific region, in close proximity to the market giant – mainland China. This article provides an overview of developments in Taiwan's pharmaceuticals industry, and discusses the influence of the National Health Insurance (NHI) payment reimbursement system on the pharmaceutical market.

Ensuring Quality

There are currently already 23 local API manufacturers that have passed Good Manufacturing Practice (GMP) inspections and most of them already have their Drug Master Files (DMF) approved by the US Food and Drug Administration (FDA).

The total turnover has reached NT$20.5 billion (US$0.63 billion) with 40 percent of products being sold overseas. The export value in 2008 demonstrated a leap from the previous year of about NT$4.9 billion (US$0.15 billion), with the US being the largest export destination, followed by Australia, Israel, Argentina, India, and Germany.

Nevertheless, Taiwan is facing challenges from global free market, especially China and India, which are the main competitors in the API export market. It also faces challenges in international patent protection. Moreover, the NHI has been making adjustments on drug prices. Once the profits of downstream drug manufacturers shrink, the selling prices of API will also be affected.

The Taiwanese government has been offering R&D incentive programs for the industry to accelerate and strengthen SMEs' competitiveness.

To remain competitive, Taiwan's API manufacturers not only need to integrate R&D resources to develop more practical, simpler and faster processing techniques in order to keep costs down – they also need to acquire international patent approval to maintain sustainable growth.

There are currently about 200 manufacturers of western medicine in Taiwan, most of which are traditional pharmaceutical companies. They are mainly active in producing generics and serve as representatives for foreign companies. While the competition of generics is heating up globally, Taiwan's generics manufacturers are encountering bottlenecks that need to be resolved.

First of all, Taiwan's market size is too small. In 2008, the value of its pharmaceuticals market was about NT$129.5 billion (US$4.0 billion), accounting for only 0.5 percent of the global market. The country's local pharmaceutical companies mainly sell their products

Drug Manufacturing

to the local market and the NHI system is the biggest and the only buyer in Taiwan.

Unfortunately, since the universal implementation of the Global Budget Payment System in 2002, the price of NHI paid drugs have been reduced six times in eight years, impacting both the local companies and their foreign counterparts. In addition, the big hospitals tend to use imported brand-name drugs and take up 78 percent of the country's pharmaceutical market share. Three out of four top pharmaceutical companies (by revenue), are foreign owned.

Avenues for Growth

As the market share of local companies decrease (market share in 2008: 22.3 percent), these companies need to find other ways to compete directly with foreign companies in the "big hospitals" sector. In terms of the scale of Taiwan's generics manufacturers, most are rather small, suggesting that these local companies must step into the global market to effectively increase revenue and size.

Taiwan's API manufacturers need to integrate R&D resources to develop more practical, simpler and faster processing techniques in order to keep costs down (Source: BPIPO)

In addition, most generics manufacturers produce similar products, making it difficult for differentiation and often resulting in price wars; or they produce a wide variety of products with small quantities of each, making it challenging to achieve economies of scale in production.

At a global level, Taiwan's pharmaceutical companies lack international marketing experience and are unfamiliar with foreign regulations. This limits their expansion into overseas markets.

Apart from the traditional pharmaceuticals companies mentioned, there are about 100 newly established biologics manufacturers, most of which are only 5-6 years old. Among them, only a few companies are doing research in the development of new biologics, whilst most of them are devoted to low-risk and high success-rate biosimilars or follow-on biologics.

Since most biologics manufacturers in Taiwan are in the early R&D stage, newly self-developed biologics are yet to be seen on the market. In terms of products, there is firstly insufficient interaction between academia and industry in Taiwan, compared to other countries. Owing to the fact that upstream research institutes lack market-oriented mindset at the beginning of drug development, their academic research results cannot be easily transferred to the downstream manufacturers or to the industry.

Secondly, Small and Medium Enterprises (SMEs) often face difficulties in fund-raising, tax filing, and recruitment, which is why the government has been offering R&D incentive programs for the industry to accelerate and strengthen SMEs' competitiveness.

Third, even though Taiwan's pharmaceuticals related regulations have caught up with global trends, the country's inspection system is not sufficiently transparent and there is a lack of precise rules.

Fourth, although local pharmaceutical companies provide more than 70 percent of the drugs in Taiwan's market, they only receive a quarter of the total drug payments made by NHI. On the contrary, foreign pharmaceutical companies get paid 75 percent of total payments but provide only 30 percent of the drugs.

This has not only resulted from the difference between the prices of brand-name drugs and generics, but also from the fact that the prices of locally produced generics are too low to create sufficient profits for local manufacturers.

With an aim to build up an industrial environment that is favorable to local pharmaceutical companies, the government needs to use the prices on the international market as a reference. It may need to set up a similarly priced baseline and revise the prices of

local and foreign drugs and the procurement system, in order to stimulate R&D in the pharmaceuticals industry.

Potential Expansion

While botanical drugs represent the smallest sector in the industry, it is however a niche market with the greatest potential for growth. Government efforts have been made in setting up regulations for Chinese medicine. For example, the "Five-year-plan for the Technological Development of Botanical Drugs" that was promulgated from 2001 to 2005, received a funding of NT$5 billion (US$0.15 billion).

This plan contributed to patent protection, clinical trials, quality control, research environment, and education, and helped to modernize TCM in Taiwan. It has transformed TCM into an area of science, with its effects and efficacy supported by technical evidence.

Since September 2005, all Chinese medicine manufacturers have implemented GMP and have significantly improved their quality of production. The total output value (sales) of Chinese medicine in Taiwan was around NT$1.3 billion (US$0.04 billion), with the domestic market accounting for 80 percent, and 20 percent being exported. Export value is gradually increasing.

In line with the global trend for botanical drugs development, many basic research institutions in Taiwan have successfully transferred their technologies to the industry, and several are already undergoing clinical trials both domestically and internationally.

Although more countries are accepting the benefits of botanical drugs and market demand is expanding, the percentage of Big Pharma companies that is focusing on this area is still low.

In general, Taiwan's pharmaceuticals industry has been making steady progress. Yet with globalization, product life cycle has been shortened, resulting in reduced profit. The industry needs to focus on overseas markets and creating products.

In 2009, 55 domestic companies have sold their products to 37 countries overseas, suggesting that local pharmaceutical manufacturers have proactively responded to the unfavorable NHI environment in Taiwan by implementing international marketing strategies.

With strict regulations in the international market, Taiwanese companies have also started to comply with cGMP and even Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) GMP, in hopes of gaining international recognition.

There are also plans for Taiwanese companies to merge and acquire foreign pharmaceutical companies, to obtain international marketing channels. In terms of drug R&D, the industry needs to look for alternatives such as focusing on developing solutions for prevalent Asian diseases and major domestic ailments, in order to position itself well in the niche market. **PA**

Enquiry code: 097E04

Taiwan's API manufacturers started up in the 1940s, with only simple processes for organic chemical synthesis. At that time, all the technologies were transferred from more advanced nations such as Europe, the US, and Japan. In 1973, the Taiwanese government realized that API is essential for the development of pharmaceuticals industry.

Hence, the National Science Council – an institution for the promotion of scientific research, and the Department of Health – the governing organization facilitating healthcare policies, were assigned to promote the R&D and manufacture of APIs.

During early 1980s, several measures were implemented, including the temporary suspension of inspection and registration, the temporary inhibiting of imports, and tariff reduction and exemption – which resulted in the successful development, commercial-scale production, and exports of several APIs.

Since 1985, in order to prepare Taiwan to join the World Trade Organization (WTO) and to follow the global trend of Intellectual Property (IP) protection, the has government revised and amended the Patent Act several times, pushing the country's API industry forward.

As a result of the advancements in the chemical and biological industries, the technologies of organic chemical synthesis, biochemical fermentation, and process enlargement have all been improved. Highly educated and trained professionals have also been nurtured.

In the last decade, the global inclination to use low-cost yet good quality generics drugs has helped Taiwan's local API manufacturers to expand their international markets.

Drug Discovery

Magnetic Beads: Automation and Reproducibility

Magnetic bead-based assay platforms offer a more efficient alternative to traditional suspension bead arrays.

Christian Zimmermann,
Bio-Rad Bio-Plex Business Unit

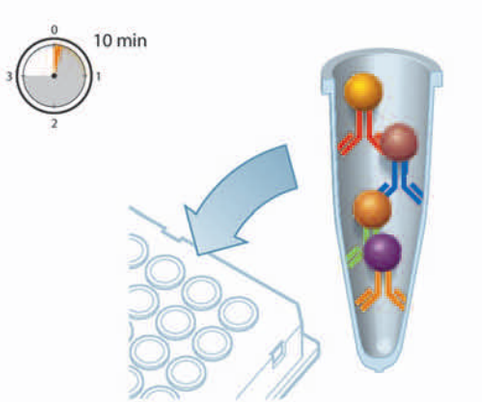
For the past 50 years, researchers have counted on immunoassays to investigate the roles of proteins and other biomolecules in a myriad of biological processes. The several thousand studies each year that cite immunoassays, attest to the impact they have had in identifying and assessing the progression of diseases including Human Immunodeficiency Virus (HIV), Alzheimer's and many cancers.

Researchers who run immunoassays know how precious limited samples can be. Advances in multiplex immunoassays have proven invaluable in helping to conserve samples by measuring multiple parameters simultaneously.

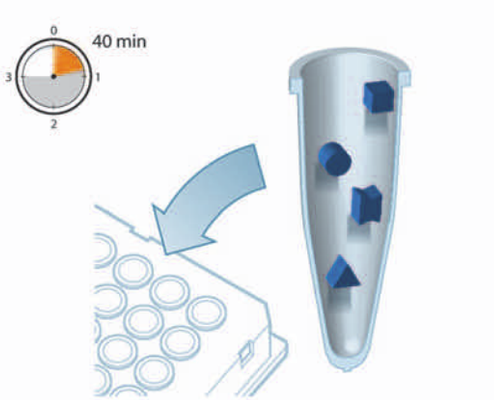
Suspension bead arrays which couple target compounds, protein conjugates or class-specific antibodies onto microscopic beads, offer a level of multiplexing for immunoassays that may not be matched by traditional Enzyme-Linked Immunosorbent Assay (ELISA) platforms.

Because of this, suspension bead arrays are replacing ELISAs in some labs. But with manual wash steps that constitute a signification portion of assay time, the speed of automated traditional suspension bead arrays pales in comparison to fully-automated ELISAs. Furthermore, manual washing can often introduce frustrating inconsistencies that compromise the reliability of assay results.

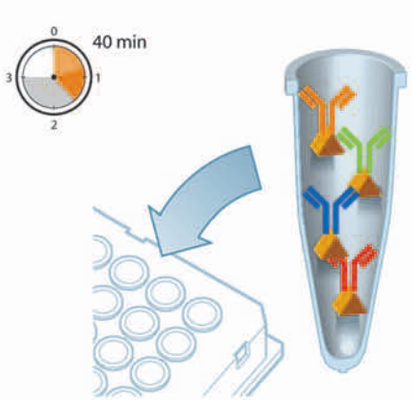
Newer magnetic bead technology has helped to overcome the limitations of manual washing. Such assays allow researchers to completely forego manual vacuum filtration steps



1. Magnetic beads are dyed with differing ratios of two spectrally distinct fluorophores, which identify the beads with different regions. Each bead is then coupled to antibodies against a different target.



2. The sample of analytes is added to the beads. Each capture bead region binds specifically with the target analyte in the sample.



3. After incubation and washing, biotin-labeled detection antibodies are added, and the bound analytes react specifically with detection antibodies against different epitopes of the antigen.

in favor of magnetic separation. Besides increasing the ease of use through automation, the magnetic innovation also increases assay precision by cutting out the variability that vacuum filtration introduces.

Multiplex Assays Compared

A major concern to researchers is that the assays they use, must be reliable for their end goal, or "fit for purpose." Among the factors to consider when choosing technology to measure multiple biomarkers are precision, sensitivity, sample throughput, multiplexing ability and cost.

Low-multiplexing, low-cost technologies include quantitative Polymerase Chain Reaction (qPCR), ELISA and Western blotting. These technologies can measure up to five biomarkers simultaneously and quantitatively.

On the opposite end of the spectrum, high-multiplexing, high-cost technology, includes Liquid Chromatography-Mass Spectrometry (LC-MS), 2-D gel electrophoresis, microarrays and Surface-Enhanced Laser Desorption/Ionization (SELDI). This allows the measurement of several hundred potential biomarkers, although results are essentially qualitative.

Suspension bead arrays fall in the middle, offering both throughput and quantitative measurement. Assay-specific proteins or ligands are coupled to beads, making suspension bead arrays flexible enough for any protein-ligand interaction.

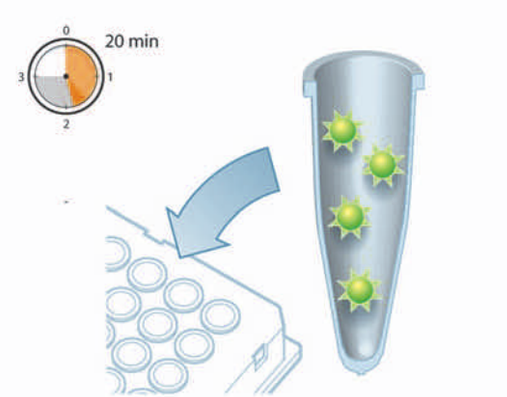
As suspension array systems can detect and quantify up to 100 biomarkers in a single sample, their quantitative performance surpasses low-multiplexing technologies with a cost per analyte that is lower than that of the low-multiplexing technologies.

Drawbacks of Traditional Suspension Bead Arrays

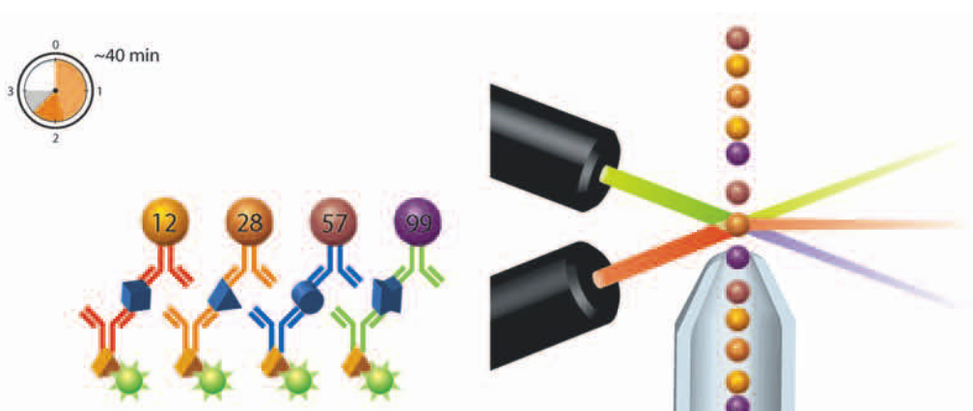
While suspension bead arrays offer major advantages in sensitivity and cost-effectiveness, the equipment used in the rest of the protocol can cause unintended consequences.

Since it was introduced more than 20 years ago, the vacuum manifold has been the standard technology for washing and removing liquid from microscopic beads. This method, however, often introduces unanticipated variables into the assay and may ultimately skew results.

First, because the vacuum source and manual pressure to the lid may fluctuate, vacuum



4. Fluorescently labeled streptavidin reporter is added, which binds to the biotin-labeled detection antibodies.



5. The suspension array system analyzes bead-captured analytes, and beads are sorted based on their regions.

- Lasers identify dyed beads by their internal fluorescent signature.
- The level of target bound to beads is indicated by the intensity of reporter signal.
- Multiplex data are reported simultaneously.

pressure can fluctuate between wells as well as between plates. If the pressure is too low, this can lead to undesired residual liquid in the microplate wells. If the pressure is too high, microspheres tend to get caught in the filter membrane.

Constant vacuum pressure that is used with liquids that vary in viscosity can lead to clogs in the filter membrane and subsequent sample loss. Vacuum pump vibrations can block filter microplate membranes. Bleed valves can create splashing if there is residual liquid in the microplate well or filter.

This is further complicated by human intervention. After using the vacuum manifold, the operator must manually add buffers and reagents and blot the base dry. Therefore, the operator's experience level can influence assay results.

Each of the above factors can introduce inconsistency into assays results. Developed out of a need for more reliable wash methods, magnetic bead-based assays can help to prevent costly mistakes by eliminating manual vacuum filtration altogether by using a magnetic wash station.

Suspension bead arrays which couple target compounds, protein conjugates or class-specific antibodies onto microscopic beads, offer a level of multiplexing for immunoassays that may not be matched by traditional Enzyme-Linked Immunosorbent Assay (ELISA) platforms.

Simplifying the Process

Magnetic bead-based assay platforms use a series of magnetic beads, each of which is dyed with a combination of two fluorophores (classification dyes) that emit at distinct wavelengths. This creates a unique spectral address for each bead. Each bead is coupled to a unique, biomarker-specific antibody.

The antibody-coupled beads serve as solid phases for the capture of analytes, followed by the binding of a second biotinylated antibody in a sandwich-like assay.

Quantitation is performed using the reporter dye, streptavidin-phycoerythrin, a fluorophore which binds to the biotin-labeled detection antibodies and emits a third distinct wavelength.

Next, the beads flow in single file and are illuminated by two lasers. Fluorescence of the particles, which emit light at three different wavelengths (two from classification dyes and one from the reporter dye), is then measured.

With an automated wash station, the filtration steps that are conventionally interspersed throughout the assay are replaced by magnetic separation. Rather than performing manual wash steps after each incubation, the beads are immobilized as they are placed in a magnetic field, allowing liquid and debris to be removed by aspiration. Once removed, the analyte, which is attached to the beads, can be measured.

Improving Performance

Using magnetic separation in automated wash technology eliminates the variability that is often associated with manual washes on a vacuum manifold that is caused by user inexperience, filter plate failure, and uneven vacuum pressure.

Overall improvements in assay consistency decrease the variability from one researcher to the next, from one plate to another and from one well to another.

With magnetic bead-based automated wash technology, assays can be completed in 3-4 minutes, and do not require additional user training. Because vacuum filtration depends on the user, assays often take a longer time to complete.

Rather that performing manual wash steps after each incubation, automated wash methods allow the researcher to simply place his or her well plate in the wash station and start the preprogrammed wash protocol.

Magnetic beads combined with an automated wash station eliminate the problems faced in filtrating highly viscous samples, which can clog filter membranes during vacuum filtration. **PA**

Enquiry code: 097E05

Treating H1N1: Innovation Behind the Science

Information technology aids in the prediction of drug development trends.

Dr Allen Yeo,
principal consultant,
IP Solutions, Asia Pacific;
Michaela White,
principal consultant,
Life Sciences, Asia Pacific,
Healthcare and Science business
of Thomson Reuters

The recent outbreak of the swine influenza virus (H1N1) has precipitated an immediate response from the international health community, governments and pharmaceutical industry alike. Global attention has focused on identifying the most effective anti-influenza drugs that are currently available and developing the next generation drugs as the H1N1 virus looks likely to continue to mutate. As stock prices of certain pharmaceutical companies such as Biota soar, the question is who the originators, current manufacturers and patent holders of these drugs are.

Of the 22 drugs that are available for the treatment of influenza virus, the Center for Disease Control (CDC) has recommended the use of Oseltamivir (brand name Tamiflu) or Zanamivir (brand name Relenza) for the treatment and/or prevention of infection with the H1N1 strain. Competitor drugs, M2 ion channel inhibitors Amantadine (Symadine, Symmetrel) and Rimantadine (FlumadDue), have not been recommended due to the increasing occurrence of mutations in the viral M2 ion channel protein and the resulting drug resistance.

So what are some of the comparative differences between Oseltamivir and Zanamivir? A Strengths, Weaknesses, Opportunities, Threats (SWOT) analysis of these two drugs reveals a competitive advantage of Oseltamivir over Zanamivir — in the method of delivery. The former offers easier oral dosage as compared to the inhalation delivery that is required for the latter. However, the latter has first-in-class status and reimbursement strategies in place for a significant portion of the US and Japan, as well as for high-risk groups in the UK.

There are 291 drugs that are related to the therapy area "Influenza Virus Infection". Using visualization tools, the current pharmaceutical pipeline for this therapy area can be viewed (Figure 1). Many of these drugs are either still in the discovery phase or have been classified as no development reported for the past 12 months. However, there have been promising drugs emerging in the pipeline – such as Daiichi Sankyo/Biota's CS-8958, which reported positive Phase II results in April 2009.

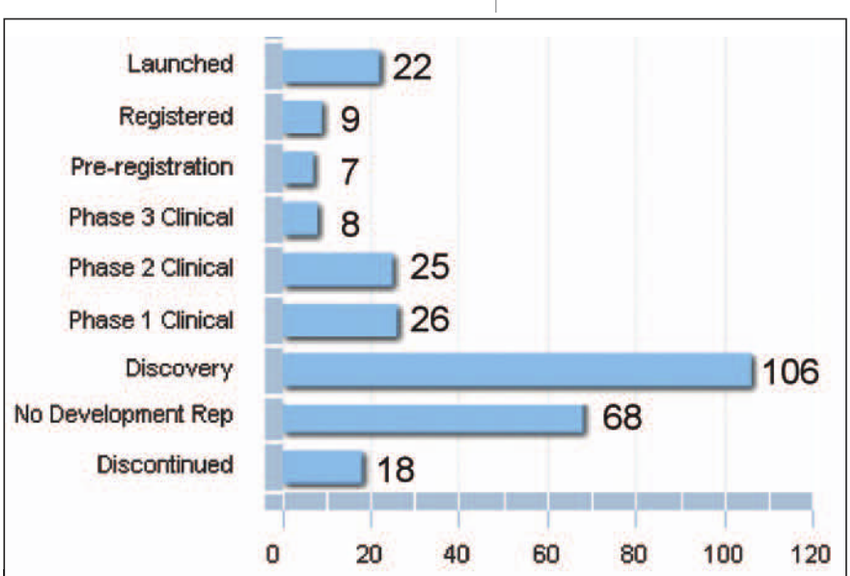


Figure 1. Number of drugs in the pharmaceutical pipeline for "Influenza Virus Infection". (Source: Thomson Pharma)

The current dominant marketers and primary patent holders for Zanamivir and Oseltamivir are Biota/GSK and Gilead Science/Roche respectively. Patents cover product, process, formulation, component of combination and delivery devices. Zanamivir patents will expire in 2013 after which generic competition can be expected. There have not yet been any paragraph IV challenges for Zana mivir. However, India-based drug manufacturers companies such as Cipla and Hetero are showing evidence of scaling up or developing Active Pharmaceutical Ingredients (API) manufacturing capabilities.

Oseltamivir patents are set to expire in 2016. Although it currently does not face any paragraph IV challenges, many generics manufacturers have shown interest in developing the drug, and competition is predicted to be fierce. Cipla

Facilitating Studies

Memory is still fresh of the world's most recent influenza pandemic 41 years ago - the 1968 Hong Kong outbreak which took one million lives, and the historic Spanish Flu of 1918-1920, which killed more than 50 million people, or 2.5 percent of the world's population. The World Health Organisation (WHO) is sparing no effort to prevent a pandemic and preparing the global population for the worst. Any type of influenza outbreak has a high mortality trend that is associated with children and the elderly. Apart from the "runny nose" symptom that is commonly associated with flu, secondary bacterial infections leading to pneumonia or bronchitis are also prevalent.

Dr Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases commented that scientists are "working on developing a vaccine with hopes of having a pilot version ready for testing in a few months".

Hence, the quest for scientific literature by scientists and national policy makers is a necessity for their fundamental understanding of the H1N1 virus as they build on past research studies to expedite the development of antiviral drugs and vaccines in order to prevent a pandemic. The uncovering of critical past knowledge also explains the impact of the H1N1 virus on humans, animals and the environment.

The world is worried about human to human transmission, whilst pig farmers are concerned that infected humans do not pass the virus on to their pigs. The Center for Disease Control and Prevention (CDC) recorded that inter-human transmission is low; there were only 12 confirmed cases between 2005 and 2009.

What about novel studies of vaccine production? Neumann has described a reverse-genetics system that allows one to efficiently generate Influenza-A viruses entirely from cloned Complementary Deoxyribonucleic Acid (cDNAs), the core replicating block of any genes. This system, which does not require helper virus infection, is useful in mutagenesis studies and vaccine production, and has received more than 300 citations in 25 subject categories spanning respiratory and cancer studies to drug development and adversity.

The comprehensive mapping of both past and current research is vital to understanding the various research applications to date. Researchers often use the "citation tree" to visualize such "revolutionary" effects to monitor and clarify related research applications and to seek collaborators. The citation tree helps researchers to visualize and understand the connection between relevant past research (cited references) and articles of subsequent influence (known as "forward citations").

The global scientific community has been reporting on H1N1-related influenza studies for many decades. There are, up to date, 1,574 related unique journal articles (or records) and conference proceedings published worldwide in Web of Science (using topic search field: "H1N1"). The top five organizations and countries studying the H1N1 virus (based on total records published) are:

NO.	INSTITUTION NAME (ABBREVIATED)	RECORDS
1	ST JUDE CHILDRENS HOSP (USA)	98
2	CTR DIS CONTROL & PREVENT (USA)	97
3	DI IVANOVSKII VIROL INST (Russia)	58
4	NATL INST HLTH (USA)	76
5	UNIV WISCONSIN (USA)	45

NO.	COUNTRY (ABBREVIATED)	RECORDS
1	USA	681
2	JAPAN	184
3	ENGLAND	164
4	GERMANY	77
5	PEOPLE R CHINA	77

Source: Thomson Reuters

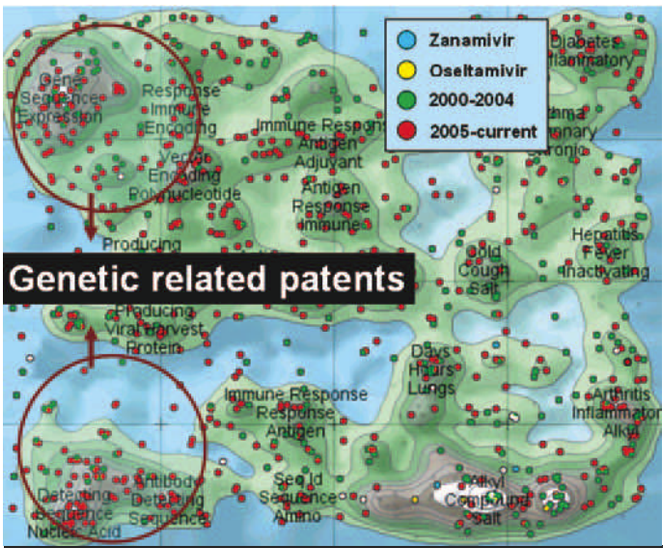


Figure 2: Themescape map of 1,324 influenza-virus-infection therapy area patent records. (Source: Thomson Innovation)

is the only company with an active US Drug Master File (DMF) and a commercially available source of API, even as five other companies have confirmed commercially available capabilities. These include Hetero and Ranbaxy of India, and Chongging Shenghuaxi and Shanghai Sunve of China.

How can one begin to understand the innovation trend and attempt to predict the future innovation of influenza and H1N1 virus-related technology through patent analysis? One way is to use a visualization analytic called the "Themescape Map". From an innovation perspective, there are 1,324 patent records (or patent families) that are related to the therapy area "Influenza Virus Infection".

Patents may be uploaded into the map software tool. Each colored dot represents a patent record that has been plotted using keywords from the Derwent patent title and abstract. The application brings technically similar patent documents into proximity clusters in order to easily understand different technology inventions.

Figure 2 also shows additional "time-slice" information of patent filing trends comparing 2000 to 2004 (330 patent records) and 2005 to current (667 patent records). It can be inferred that R&D has been more intense in the last three years for influenza virus vaccines and related technology, as seen in the two-fold increase in the rate of patent filings over the last eight years; particularly in patents that are related to genetic studies. The map can also isolate trends of assignees and inventor filling patterns to help in strategic business planning.

In addition to vigilance and screening by global health organizations, such an analysis shows that R&D continues its pace to aid in fighting the threat of an epidemic. **PA**

Enquiry code: 097E06

LIMS: From Laboratory to Management

Integrated and purpose-built Laboratory Information Management Systems (LIMS) help to facilitate data management at an enterprise level.

Dave Champagne,
VP & GM,
Informatics,
Thermo Fisher Scientific

Pharmaceutical companies need tools that help them to improve enterprise-wide communications, reach critical decisions faster and produce timely, accurate reports on how compounds are progressing. These goals need to be achieved while maximizing return on investment, shortening the pipeline life cycle and cutting costs.

System Integration

The challenge is to successfully streamline and integrate the flow of data so that management has the information that they need to make timely decisions. Pharmaceutical companies should not delay the implementation of next generation tools to help them to manage the increasing amount of data that is generated by their organizations. The solution begins with a purpose-built, enterprise-level Laboratory Information Management System (LIMS). Working with multiple, disparate systems with minimal to no integration is not a viable option.

Historically, industry standard LIMS have only delivered 30-40 percent of specific functionality that is targeted to each user's needs, requiring extensive customization to make that LIMS function in that particular setting. Such customization is commonly only possible through the use of proprietary programming languages that are developed and provided by the vendor.

The combination of minimal industry-specific functionality and often out-dated and/or costly proprietary languages has been particularly troublesome in the pharmaceutical industry. In addition, pharmaceutical laboratories normally create their own user documentation, design documentation, validation scripts, and help files. As a consequence, the implementation of LIMS in various laboratory settings has often been a long, costly and painful process not only during installation, but also in operating and maintaining the system over the years.

The growing mandates of global regulatory compliance and long-term data traceability, as well as the complexity of laboratory testing and emphasis on batch versus sample management, have forced pharmaceutical manufacturers into lengthy, expensive adaptations of generic LIMS to meet their specific requirements.

Extensive and costly customization, validation and implementation periods, in many cases lasting 36 months or more, have become routine, resulting in decreased productivity. However, with the increasingly higher costs of bringing a new drug to market, pharmaceutical manufacturers cannot afford delaying the implementation of next generation tools that will increase productivity.

The Business Challenge

With drug development times of approximately 15 years and subsequent costs approaching US$2 billion by 2010, pharmaceutical companies are increasingly in search of processes that can help them to consistently deliver a return on investment during the patent life of a drug.

Drug Development

Enterprise-level LIMS are key contributors in this effort. Delivering functionality that is specific to each stage of the drug development process, purpose-built LIMS streamline processes help to reduce costs, and present organizations with unique integration opportunities.

Such systems deliver real-time analysis and reports, and facilitate regulatory compliance and product quality. They also integrate with the company's broader network and provide secure access to key data throughout the organization.

LIMS deliver real-time analysis and reports, and facilitate regulatory compliance and product quality. (Source: Thermo Fisher)

Purpose-built LIMS for pharmaceutical applications are particularly relevant. According to the 2008 "Strategic Analysis of the US Laboratory Information Management Systems Market" by Frost & Sullivan, preconfigured solutions with test methods for specified industries will drive growth across all markets.

Greater functionality in the out-of-the-box core product means less risk, lower costs and less time involved in the implementation, validation and support of the applications. The objective of purpose-built LIMS solutions is to deliver as much domain-specific functionality as possible that addresses the critical needs of the laboratory and delivers the increased enterprise-level access that multi-site/multi-user organizations are looking for.

According to the same report, market growth indicators for solutions providers are focused on providing customers not only with purpose-built systems that are fully integrated with other laboratory equipment, but also with LIMS that easily align with global enterprise solutions.

Facilitating Data Management

A coherent strategy that can integrate data from a LIMS, Chromatography Data System (CDS), Enterprise Resource Planning (ERP), Manufacturing Enterprise System (MES), Electronic Laboratory Notebooks (ELN), and other sources across the enterprise is a key business driver.

Modern LIMS serve as common platform frameworks that other informatics solutions, instrumentation, enterprise systems and enterprise communications tools can plug into to share common functions, without having to build them from scratch for each product.

Seamless enterprise-wide integration is a necessity because it enables key knowledge originating in the laboratory to be available to management in real-time. Integrating the enterprise will facilitate better planning, data quality, collaboration and end-to-end report generation, all with the goal of providing management dashboard views of key business metrics – which are essential to effectively run operations, and thereby enabling management to have the critical data they need before, not after, any point of crisis.

The world of laboratory informatics is changing to meet the needs of pharmaceutical companies, which are continually searching for ways to reduce costs, accelerate time-to-market and respond to increasing regulatory requirements. LIMS can help pharmaceutical companies to respond with greater certainty to the unforeseen challenges that can often make or break a company.

Enterprise level integration is particularly relevant in today's business climate where near instantaneous response is required by pharmaceutical companies to protect the public and the environment. LIMS can help to bring key business knowledge originating in the laboratory to management at all levels of the enterprise. **PA**

Enquiry code: 097E07

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

The Chinese pharmaceutical industry presents opportunities for both locally based companies and multi-national corporations.

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

China with its population of about 1.3 billion, is expected to become the world's leading consumer of pharmaceuticals by 2020. In 2006, the market size was US$13.1 billion for Western-style medicines. It is currently growing by about 30 percent per year, according to Datamonitor.

The country's domestic market is expanding due to the rising number of middle-class families with increased access to healthcare. In addition, reforms have expanded distribution channels. Prescription drugs continue to represent a large opportunity, while Over-The-Counter (OTC) medications are also seeing growth, with increased awareness of self-medication, rising disposable incomes and large numbers of uninsured.

The Chinese domestic pharmaceutical industry is highly fragmented, with a number of smaller local players accounting for about 70 percent of the country's overall drug market. However, a process of consolidation has started.

Quality of Life

The rising number of middle-class families with increased access to healthcare due to changing life styles, are triggering interest from global investors. The growing use of Traditional Chinese Medicine (TCM) is complemented by Western products.

More stringent government standards and controls, stronger Intellectual Property Rights (IPR) protection and the return of Western educated Chinese with technical and management skills are additional contributing factors for growth.

China has three major areas of concentration for pharma R&D centers: Beijing, Shanghai, and Guangzhou. (Source: Frank Floether)

About 98 percent of China's drug products are still generic copies. There has been an increase in the number of Drug Master File (DMF) filings (approximately 75 in 2005) with an effort to follow the Indian model, ie, approximately 1-5 years away from Abbreviated New Drug Application (ANDA) filings.

Sinopharm has, under the control of central government, 10 wholly owned subsidiaries or shareholding companies. Sales in 2004 were US$2.3 billion with an import/export volume of US$500 million.

Zhejiang Hisun (one of the largest bulk manufacturers for antibiotics, anti-tumor and statins API) exports more than 80 percent of API production to

Drug Development

the EU/ US. Other major players are Zhejiang Huahai, Shanghai Fosun, Harbin Pharma, SJZ Pharma Group, Hisun Pharma SPG, Hengdian Group, Neptunus, Shandong LuNan, Yangzijiang and Founders Group.

China is committed to building and expanding the pharmaceutical industry, with strong support from the government. At the same time, there are also foreign Multi-National Corporations (MNCs) operating in China with large R&D budgets and global resources.

For example, the government is building science parks, like the Zhangjiang science park ("Drug Valley") in Pudong, Shanghai. Eli Lilly and Roche have R&D facilities at this location. Another development zone is the Tiajan Economic Technology Development Area (TEDA) in Beijing.

Efforts have been made to attract talent back from the West. Like India, the reverse "brain drain" is fuelling the build-up of Chinese talent. As an example, the Guangzhou Institute of Biomedicine and Health is actively recruiting scientists, with a strong preference for those who have had international experience.

Prescription drugs continue to represent a large opportunity, while Over-The-Counter (OTC) medications are also seeing growth, with increased awareness of self-medication, rising disposable incomes and large numbers of uninsured.

Government Assistance

Since 2004, foreign–invested, Shanghai–based firms are eligible to receive subsidies for newly patented technologies and/or methodologies that are used in new products. Previously, only domestic firms could apply for these subsidies. These funds can represent up to 75 percent of R&D costs, if the latter is performed in Shanghai.

China has created an attractive tax environment, ie, 20 percent for foreign companies, compared to 33 percent for domestic companies. This is about to be revised (foreign: 24 percent, domestic: 28 percent). However, favorable tax incentives will still apply for R&D collaborations with Chinese research institutes and for those R&D companies that are registered in the High-Tech Development Zones (HTDZ). Incentives seem to be more attractive in Shanghai's HTDZs compared to those in Beijing.

Along with Beijing, Shanghai is a popular location for foreign-owned pharma R&D centers, due to its growing variety of other businesses that provide services to the pharmaceutical industry. Tax concessions and access to capital at favorable rates are in addition to direct savings on facilities, overheads and salaries.

The Chinese domestic biotechnology industry has become one of the largest and most productive in Asia (eg, the world's first licensed gene therapy medication was developed by Shenzhen-based SiBiono GeneTech in 2003).

Contract Research Organizations (CROs) are becoming an increasingly important component of the drug development industry. Chinese CRO growth is outpacing that of the industry. A growing number of foreign and domestic CROs are also establishing operations in China.

China's top ranking emerging CRO is WuxiPharmatech. It was founded in 2001 and has grown to over 900 staff. It claims that its current customers include 18 of the top 20 pharmaceutical companies and eight of the top 10 biopharmaceutical companies in the world. Ranking second is ChemPartner, which was founded in 2003 and has grown to 400 staff. Its customers include Eli Lilly, Merck, and other top 20 global pharmaceuticals companies.

China and Singapore and amongst the countries that are alternatives to India for conducting pharmaceutical R&D. Whilst China is of strategic importance as a market and offers low labor costs, Singapore mainly attracts companies by tax incentives and infrastructure.

Attracting Investment

China is a somewhat challenging country in which to conduct business, due to its

varied culture and business environment. There are several reasons for conducting R&D in China:

- **Supportive government policies**
  - o Building infrastructure to support biopharmaceutical R&D (industrial parks)
  - o Tax incentives
- **Large talent pool and well-educated workforce**
  - o 4.5 million university graduates annually
  - o Bench scientists with few major knowledge gaps
- **Academic research**
  - o Competent professionals
  - o Productive collaborations are possible with proper guidance
- **Low cost structure** – In particular low cost of conducting clinical trials, due to low labor costs and speedy clinical trial recruitment. However, as low-cost labor will not always be available, companies that decide to stay for the long-term should consider quality, market share and talent pool.
- **Quick entry to the fast growing Chinese market**
- **Huge naive patient population**
- **Abundant preclinical animal resources**
- **Rich Traditional Chinese Medicine (TCM) / natural medicine knowledge**

Drug Development

There are also challenges to consider:

- China's SFDA (State Food & Drug Administration) approval process tends to be lengthy, with a lack of transparency
- Language barrier resulting in delays in communication and compromising cost advantages (eg, by the use of interpreters)
- Import tax for instruments and reagents
- Weak IPR (trade secret, patent protection, confidentiality agreement, etc)
- Lack of experienced R&D personnel
- Competition for talent in focal areas such as Shanghai
- Limited GMP experience relating to GMP sensitive areas such as full development (eg, analytical and formulation)
- Dealing with government bureaucracy

A strong driver for choosing China, is the country's generally strong economic growth and its national reimbursement list.

India should be seen as a complement rather than an alternative to China in terms of conducting R&D. Therefore, an evaluation of pros/cons for offshoring R&D between China and India may not be practical as it depends on strategic intent, the type of R&D activity, business model and other factors that have been discussed.

Investment Decision

Where to offshore or to invest depends on the importance of several factors:

- **Strategic intent**
  - o Cost savings
  - o Market access/potential
  - o Access to talent
- **Type of R&D activity**
  - o Clinical
  - o Medicinal chemistry
  - o Chemical & pharmaceutical development
- **Risk tolerance**
  - o Exposure to IPR risk
  - o Operational risk
  - o Investment risk
- **Payback time**
  - o Short term returns
  - o Long-term investments

According to an Economist Intelligence Unit (EIU) survey which involved 104 senior executives across industries worldwide, China and India are emerging by far as the top favorable destinations outside of their home countries for R&D spending.

A strong driver for choosing China, is the country's generally strong economic growth and its national reimbursement list. In India, the focus is on the public procurement of generics.

MNC Activity

In 1985, Janssen Pharmaceutica (Johnson & Johnson) was the first Western pharmaceutical company to set up a pharmaceutical factory in China (Xian). By 1983, the company had signed a cooperation contract to modernize products in an existing, but old, chemical factory in Hanzhong. Xian Janssen is one of China's top joint ventures with a turnover of about US$400 million in 2006 and more than 1,500 employees. Novo Nordisk inaugurated the first international R&D centre in China in 2002.

Over the past few years, the pace of expansion into China has accelerated, with 38 foreign pharmaceutical companies now operating in the country. Of these, AstraZeneca, Eli Lilly, Novo Nordisk, Pfizer and Roche run their own clinical trial centers in China, with much of their activities being centered around Shanghai.

The decision by companies to move into Shanghai reflects the city's growing reputation as a technology hub. Apart from what has been called the best physical infrastructure in China and an expanding base of several hundred biotechnology and medical enterprises, many foreign chemical and pharmaceutical companies have set up their operations in Shanghai. These companies include Degussa, Dow Chemical, DuPont, Honeywell, Pfizer, Roche and Toray Industries.

The Roche center was inaugurated in 2004 and now employs 80 people including 56 scientists. Of these, about one-third are Western-trained scientists of Chinese origin who have returned home. According to Roche, the facility may eventually employ as many as 250 drug discovery scientists.

Roche has announced its decision to build a second R&D site in China, spending US$100 million to create the first fully functional China clinical drug R&D center that is owned by a pharmaceutical MNC.

Pfizer has invested US$500 million, amongst plants in Dalian, Suzhou, and WuXi and also in a clinical trial center.

In November 2006, Novartis announced the construction of a 400-person, 38,000 sq meter Shanghai R&D center (Zhangjiang Hi-Tech- park, close to Roche's center), reflecting a US$100 million investment while at the same time building an API plant in Jiangsu province.

Prior to the establishment of the center, the company had been bringing European experts into China to establish centers in hospitals with good clinical practice. This was to allow it to conduct clinical trials in China in collaboration with Chinese partners such as, the Shanghai Institute of Materia Medica, WuXi PharmaTech, Chinese University of Hong Kong National Institutes of Biological Sciences, and Kunming Institute of Botany.

More stringent government standards and controls, stronger Intellectual Property Rights (IPR) protection and the return of Western educated Chinese with technical and management skills are additional contributing factors for growth.

Cooperative Research

Similarly, Wyeth unveiled its first R&D facility in China in 2006. The Shanghai-based center will act as the company's regional clinical development center in Asia. To augment the center's in-house capabilities, Wyeth has established a joint early clinical development center with Peking Union Medical College Hospital in Beijing.

Eli Lilly is headquartered in Shanghai with offices and facilities in Shanghai, Beijing and Guangzhou,. The company established a joint venture in Suzhou and wholly owned it in 2002. Its Suzhou manufacturing plant and Shanghai research center together employ about 1,000 staff.

Its 250 Chinese chemists, which represent the largest of its non-US drug development teams and about 20 percent of its overall scientific staff strength, are working in all stages of drug development. Lilly intends to reduce its global R&D budget from about US$3 billion in 2006 to US$800 milion by 2010.

The company aims to achieve this through joint research with Chinese and Indian organizations. In China, Lilly has been working with ChemExplorer in Shanghai on molecule selection since 2003, and now outsources 20 percent of its discovery work to the latter. In 2007, Lilly also entered into a strategic partnership with Hutchison MediPharma (HPML).

GSK is planning to establish and invest US$40 million in a stand-alone R&D center, devoted entirely to discovering innovative drugs and healthcare solutions. Its first production plant was setup in China 22 years ago, and the company has small R&D units in Beijing,

Drug Development

Shanghai and Tianjin. It spends 17 percent of its sales on international R&D every year. While GSK already uses China as a manufacturing hub to produce medicine, its center will allow the development of new end-to-end products.

Merck is also active in Shanghai, although its presence is largely through R&D collaborations rather than its own in-country staff. In 2006, the company announced an agreement with Shanghai Biochip on genetic and biotechnology research for cancer treatment. The agreement is for the collaboration of an oncology research program.

In 2006, AstraZeneca set aside US$100 million for a R&D center called Innovation Centre China ICC, to start operations in 2009, while also investing into their manufacturing site in WuXi.

Beginning 2009, Bayer Schering announced that it will be strengthening its global R&D capabilities through the foundation of a global R&D center in Beijing. The company will invest some 100 million Euros (US$147 million) over the next five years to establish the center.

Servier, one of the largest independent French pharmaceutical companies, has set up a joint venture with Tianjin Huajin Pharmaceutical in Tianjin after already establishing a R&D company in Beijing in 2001.

Some drug developers are seeking to expand their activities to include traditional Chinese medicines. In 2006, for example, Merck entered into an agreement with Chi-Med's Shanghai research center, giving the former access to the latter's library of botanical compounds.

Headquartered in Beijing, Novo Nordisk has about 1,000 employees in China and has become a leader in diabetes products in the country with fully integrated R&D, production, sales and distribution. The company has also announced an investment of another US$10 million in Beijing for a biotech development center. **PA**

Singapore: Setting the Stage for Expansion

Singapore's government has formulated a strategic objective to enable the country to become a center for the pharmaceutical, biotechnology and medical- technical industries. Besides tax incentives, a world-class infrastructure, political stability and its IPR protection record, Singapore offers highly professional authorities – amongst them the Singapore Economic Development Board (EDB) that supports investors and companies that are considering to set up a presence in the country.

Many pharmaceutical MNCs, amongst them GSK, Sanofi-Aventis, Merck ,Pfizer, Schering – Plough, Johnson & Johnson and Wyeth have invested in Singapore with their own R&D centers, manufacturing facilities, marketing and distribution hubs or support functions such as Information Technology (IT) or finance.

In recent years, Pfizer and Schering-Plough have initiated API plants in which they have invested several hundred million dollars each. Merck moved its Asian regional headquarters from Hong Kong to Singapore in 2007 because of the latter's favorable business environment.

Eli Lilly announced in 2007 to triple the size of its existing research center in Singapore with an investment of US$150 million. In total, the MNCs in Singapore are estimated to employ more than 3,000 staff.

One drawback of the country is (besides the absence of a domestic market) the fierce competition for experts and scientists.

This could mean that the currently relatively low labor costs will rise, as the surrounding countries are unable to provide the growing need for qualified human resources. At the same time, there is an increasing number of MNCs that are entering the country or that are expanding their presence.

However, the attractiveness of Singapore for expatriates from the West and the influx of foreign experts still compensates for the shortfall, to an extent. Singapore is particularly attractive for MNCs, because the saving potential for their pricey products is provided by tax incentives that are offered by the government.

Enquiry code: 097E08

Part three of this series will be featured in the November/December issue of PharmaAsia and will focus on a comparison between India, China and Singapore.

Product Focus
Cellular Reagents

Thermo Fisher Scientific Introduces Reagent Kit for Cell-Based Image Analysis

The Cellomics Synaptogenesis High Content Screening (HCS) reagent kit from Thermo Scientific enables the simultaneous detection of neuronal population, neurite, pre-synaptic vesicle, post-synaptic puncta and synapse. This is achieved by using a fixed end-point assay that is based on immunofluorescence detection in cells that are grown on standard high-density microplates.

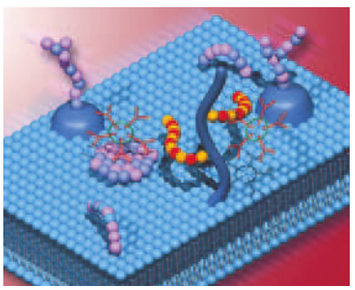
The reagent kit has been designed to enable drug discovery and systems biology researchers to measure synaptic function by utilizing the technology in high-content cell-based image analysis. The kit has been optimized with a ArrayScan HCS reader. The reader uses the Neuronal Profiling BioApplication software module to identify the synapse measured by the colocalization of the pre-synaptic marker with the post-synaptic marker.

The kit has been validated in cellular imaging assays for reliable and reproducible results and works on all HCS platforms, offering flexibility in end-user instrumentation. In addition to HCS instruments, cells that are labeled by the kit reagents can be viewed and analyzed by other fluorescence microscopes. The kit also saves valuable research time because it requires no optimization of assay development.

Thermo Fisher Scientific, www.thermo.com

Enquiry code: 097P01

Detection of Heparanase in Cell Culture



Heparan sulfate proteoglycans (HSPG) are known to play important structural and functional roles in linking the component proteins of the basement membrane, controlling the permeability properties of the membranes and signal transduction.

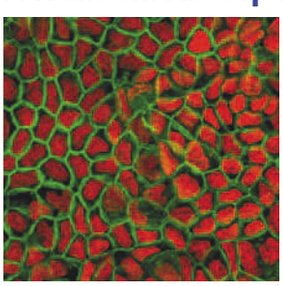
To date, a handicap in HSPG research has been a lack of a sensitive and more importantly specific test for human heparanase activity. Furthermore HSPG research has also suffered from a lack of a purified enzyme or instability of the cloned enzyme limits assay design.

To address these shortfalls, amsbio has launched non-radioactive assay kits that offer the sensitive and specific quantitative detection of heparanase in cell culture supernatants, human plasma, biological fluids and tissue samples. Supplied in a convenient 96-well plate format, the kits are easy-to-use.

amsbio, www.amsbio.com

Enquiry code: 097P02

Advancell: Absorption and Oral Toxicity



Advancell develops, produces and commercializes cell-based in vitro models with predictive and regulatory value, to prove the efficacy, security and action mechanism of new molecules.

Some of the in vitro models that are offered in the form of services, are produced in a "ready-to-use" format. They are distributed as investigation kits to R&D departments, with the aim of increasing efficiency and reducing the costs associated with the development process.

Cacoready from Advancell is a ready-to-use, cell-based model of the human intestinal barrier, that allows the prediction of absorption and oral toxicity to the body of different molecules. It can be applied to the evaluation of the oral bio-availability of drugs in development as well as to the determination of the toxic effect of compounds.

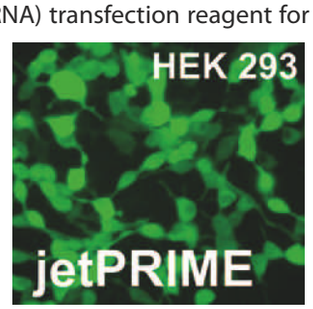
The proprietary IsoCyp technology provides solutions to predict the potential toxicity of metabolizing products of new molecules that enter into contact with the liver. This range of products allows the security of new drugs to be evaluated at an early stage.

Advancell, www.advancell.net

Enquiry code: 097P03

Polyplus-Transfection Introduces Transfection Reagent

Polyplus-transfection has introduced jetPrime – a versatile and powerful Deoxyribonucleic Acid (DNA) and small interfering Ribonucleic Acid (siRNA) transfection reagent for day-to-day experiments, transient expression studies as well as RNA interference (RNAi) gene silencing.



The reagent is easy-to-use and is compatible with serum and antibiotics. It ensures high DNA transfection efficiency (70–90 percent) in a wide variety of adherent cells. Transfection only requires small amounts of plasmid and reagent, eg, 2 µg DNA and 4 µl jetPrime per well in 6-well plates.

In addition to reducing costs, using less DNA also minimizes adverse cytotoxic effects that are triggered by transfection. The reagent leads to over 90 percent knock-down of endogenous gene expression in a variety of cell lines.

Polyplus-Transfection, www.polyplus-transfection.com

Enquiry code: 097P04

Calendar of Events

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

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

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

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

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

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

Oct 27 - 28, 2009
4th Annual Generics Asia Summit 2009
Singapore
www.ibc-asia.com/generics

Oct 28 - 29, 2009
Asia Biomanufacturing Summit 2009
Singapore
www.asiabiomanufacturing.com

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

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

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

Nov 16, 2009
Generic Medicines: IP / Legal and Regulatory Issues
Mumbai, India
www.management-forum.co.uk/pharmaceutical/eventid/1109

Nov 18, 2009
Generic Medicines: IP / Legal and Regulatory Issues
Delhi, India
www.management-forum.co.uk/pharmaceutical/eventid/1109

Nov 20, 2009
Generic Medicines: IP / Legal and Regulatory Issues
Hyderabad, India
www.management-forum.co.uk/pharmaceutical/eventid/1109

Nov 30 – Dec 2, 2009
Logipharma Asia 2009
Singapore
www.logipharmaasia.com

Dec 1 – 4, 2009
biologic India 2009
Mumbai, India
www.terrapinn.com/2009/bioindia/

Dec 3 - 4, 2009
2nd annual Sales & Marketing Conference China
Shanghai, China
www.eyeforpharma.com/china

Dec 10 – 11, 2009
2nd China International Pharmaceutical Summit 2009
Beijing, China
www.chinapharmasummit.com

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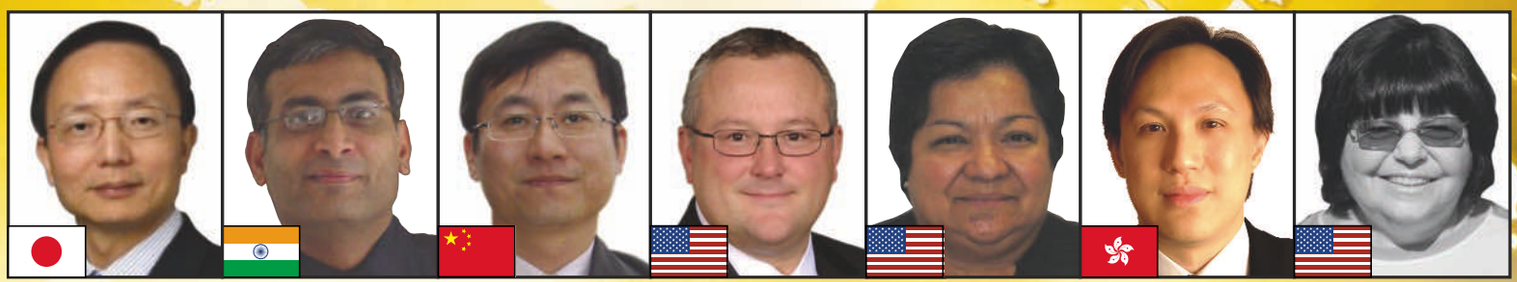

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– CenterWatch, March 2008

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