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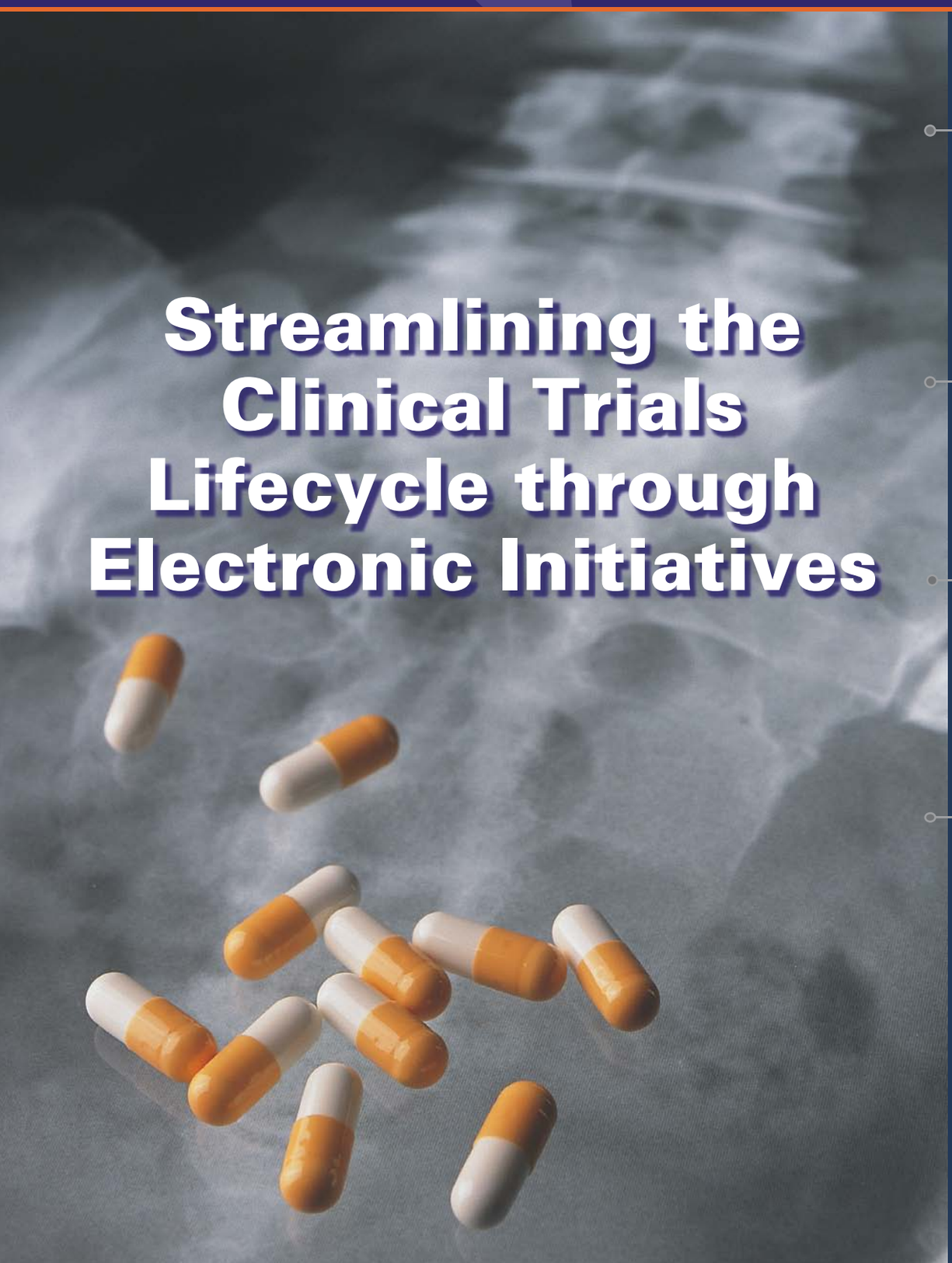

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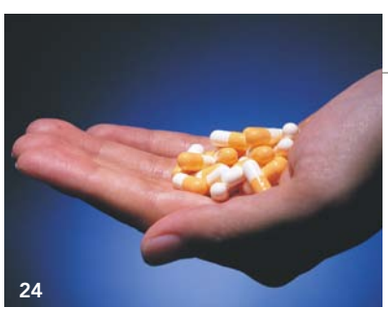

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Editor's Note

Michael Tham
Editor

Taking Center Stage

Low labor costs, availability of raw materials and the ambition for international recognition – these seem to be some of the ingredients of success for more than a few China-based pharmaceuticals companies. In the May 2009 edition of API/Interphex China (page 37), interviewees of selected local companies reveal that they have expanded into overseas markets. For one, Feng Sheng Xi, deputy director of BYS tells us that export markets account for 20 percent of her company's product.

This trend has also been observed from the show which in the past has been predominantly China-centric and focused on domestic trading. With globalization, the needs of the industry are evolving and many exhibitors are now focusing on ways to sell their products to overseas markets.

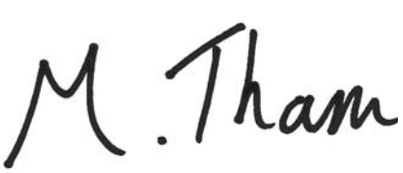
The strengthening of Sino-India ties also seems to be another current trend. For example, India-based companies account for 30-40 percent of China-based, Qilu Pharmaceutical's exports.

According to Chirag Doshi, hon secretary, The Indian Drug Manufacturers' Association, about 60 percent of the global API supply comes from China.

For Asian pharmaceuticals suppliers that aspire to expand beyond domestic markets, adhering to Good Manufacturing Practice (GMP) guidelines is also necessary for attracting buyers from foreign lands.

On the other side of the world, western agencies such as the European Medicines Agency (EMEA) and the US Food and Drug Administration (FDA) are working towards ensuring GMP compliance via onsite inspections of drug manufacturing facilities in Asia.

It appears that the success of many Asian pharmaceuticals companies is heavily dependent on their ability to produce drugs that comply with international manufacturing standards. Already, many have obtained certification from various regulatory bodies and have moved beyond their domestic playing fields – and more can be expected to follow suit in the coming years. **PA**



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46121 PA

UK Budget Heralds Price Cuts on Branded Pharmaceuticals

As part of the UK government's drive to save £2.3 billion (US$3.4 billion) in the National Health Service (NHS) during 2010–11, £550m will be cut from the prices of branded drugs as a result of the revised Pharmaceutical Price Regulation Scheme (PPRS). Consequently, with the volume of branded drugs having remained flat over the last four years, the total sales of the UK branded pharmaceutical industry are forecast to decline from 2009 onwards.

Due to the global economic downturn, branded pharmaceuticals sales are already suffering in countries such as the US, which lack a nationalized healthcare system. The rising number of unemployed and therefore uninsured patients are switching to cheaper generic drug alternatives. As a result there will be a knock-on effect on branded prescription drug sales, which are now forecast to decline by one to two percent in 2009.

This is not the case however in the UK, where patient out-of-pocket costs are capped at £7.20 for prescriptions of either generic or branded drugs (where no generic is available). Moreover, in many cases the prescription charge is waived due to the financial status of the patient. Nevertheless, the global economic downturn has exacerbated the challenges that branded pharmaceuticals face in the UK market.

In the UK, generic drugs are responsible for 65 percent of drug volume and 25 percent of sales. Generics uptake is set to rise as many branded products lose patent protection in the UK within the next decade. More than 87 perent of prescriptions are written generically, with the remaining 13 percent likely attributable to branded biologic drugs which are yet to face non-branded 'biosimilar' competition.

Furthermore, generic substitution by pharmacists will become mandatory from 2010, unless the physician has ticked a "do not substitute" box.

The branded industry will be compensated by price increases of 0.1 percent in January 2011, 0.2 percent in January 2012, and 0.2 percent in January 2013. The government has also announced a £750m Strategic Investment Fund to support industrial projects of strategic importance, which can potentially be accessed by struggling UK biotechnology companies. However, with £250m earmarked for low-carbon investment, the £500m to be allocated across the rest of UK R&D is too little, and too late for small biotechs.

On top of the PPRS price cuts and the growing genericization of small molecule drugs, branded pharma now faces threats from biosimilars (generic versions of biologic drugs), which are expected to enter the UK market, providing a lower cost alternative to branded biologics. **PA**

Atherosclerosis Vaccine Development Receives EU Support

Vienna-based AFFiRiS has announced that its atherosclerosis vaccine development program is receiving support from the EU's Eurotrans-Bio call.

The supported project – known as CETP Vaccine (ETB-2008-28), is based on the Affitome technology of the former and is being conducted together with EMC microcollections from Tübingen, Germany.

CSO Dr Frank Mattner explains: "Today's therapies with Statins act on low density lipoprotein cholesterol (LDLc) and reduce the latter's concentration in the blood. This type of treatment can reduce the likelihood of severe heart disease by as little as 30 percent – and that's only if the patient takes the necessary medication correctly and regularly. In contrast, our vaccine approach aims at decreasing the cholesterol transfer from HDL to LDL, thereby increasing the concentration of the beneficial HDL. This vaccine approach with its long-lasting effects should avoid patients having to take life-long, daily medication to a strict regimen."

The main item of the joint efforts of AFFiRiS and EMC is the vaccination against cholesteryl ester transfer protein (CETP). By transferring cholesteryl ester from HDLc to LDLc and VLDLc, this protein reduces "good" HDL and has a detrimental impact on the ratio of LDLc to HDLc. In the future, the vaccine will reduce the

activity of this protein and shift the balance of HDLc and LDLc in the blood back in favour of HDLc.

Project manager Dr Sylvia Brunner adds, "CETP is one of the body's own proteins. In trying to reduce its activity using a vaccine, we are faced with a formidable challenge. The body has many means of suppressing an immune response to its own proteins, or limiting the effectiveness of any such response. That's why previous attempts to develop a vaccine against CETP failed. However, as AFFiRiS has already demonstrated in its work on a vaccine for Alzheimer's disease, the Affitome technology makes it possible to circumvent these mechanisms. We are now applying this principle to atherosclerosis." **PA**

Frost & Sullivan Awards Asia Pacific Companies

Frost & Sullivan presented 20 awards to the best companies in Asia Pacific's Healthcare sector at the Asia Pacific Excellence in Healthcare Awards held at the InterContinental hotel in Singapore.

Held for the fourth consecutive year, the awards banquet recognized companies across pharmaceuticals, clinical diagnostics, imaging, generics, biotech, clinical research organisations and medical devices sectors.

Recipients of the awards included Ahmet Genel, MD, Pfizer; Mark Engel, chairman, Excel Pharmastudies; Elmo de Alwis, CEO and MD, Sigma Pharmaceuticals; Dr Wim Botermans, Regional MD, Asia, IBA Health; Grace Park, Singapore country director, Medtronic; Tony Wilkey, CEO, Prudential Corporation Asia.

Reenita Das, senior VP for Healthcare practice at Frost & Sullivan Asia Pacific, commented that the healthcare sector in Asia is expected to perform better than its counterparts in the US and Europe in the coming years. She predicts that Asia will take up about 25 percent of revenues in the next three years, from its current level of approximately 18 percent.

Elaborating on the likely cause for this shift, Reenita said, "Asia has evolved to become the new frontier for pharmaceutical firms in search of their next blockbuster drug while keeping research costs low. Companies need to set their strategic sights on a future global environment where Asia will not only be a product market, an outsourcing center or a manufacturing powerhouse but also a key component of drug discoveries and high-end innovation." **PA**

Baxter to Expand Manufacturing Operations in Singapore

Baxter International has announced its plans to expand its existing Singapore manufacturing operations with the addition of a new bulk production facility for Advate [Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method] – the recombinant factor VIII (rFVIII) that is free of blood-based additives, for people living with hemophilia A.

The needs of the global hemophilia community are changing due to improving standards of care in emerging markets, increased prophylactic use of rFVIII therapies and the fact that the life expectancy for hemophilia patients has increased from 11 years prior to the 1960s to more than 60 years today.

The company plans to enhance its manufacturing capabilities in Woodlands, Singapore. **PA**

Cover Story

API Manufacturing: Complying with International GMP Regulations

Asian Manufacturers of Active Pharmaceutical Ingredients (API) have to adhere to Good Manufacturing Practice (GMP) guidelines in order to penetrate Western markets.

Dr Stefan Kettelhoit,
GM,
blue inspection body

The majority of medicinal products manufactured in Europe and the US contain Active Pharmaceutical Ingredients (APIs) and excipients which have been manufactured in Asia. In recent years, these active and inactive pharmaceutical ingredients have become increasingly available globally as trading goods. This has often resulted in the non-compliance of APIs with the predefined and specified quality standards, affecting the safety and the health of patients who consume products that contain such ingredients.

Falling Short

There are many reasons for the deviations from quality standards. For example, physicochemical properties may have changed; the stability of the substance or the pharmacological activity might have been impaired or the impurity profile may have been aggravated.

Extensive analyses of the finished API cannot sufficiently address these problems as they cover "expected" deviations and impurities and only detect specified items. In 2008, the Heparin product scandal was caused by oversulphated chondroitine sulphate that avoided detection as a contaminant in quality control tests.

European manufacturing authorization holders are obligated to ensure Good Manufacturing Practice (GMP) compliance of their medicinal products. This is laid down in Article 46f of "Directive 2001/83/EC", which has been transformed into the national legislation of the European member states. Corresponding regulations in the US can be found in section 501(a)(2)(B) of the "Federal Food, Drug and Cosmetic Act".

Misinterpretations can be avoided by employing experienced auditors who are familiar with the regulatory guidelines in India and China. (Source: blue inspection body)

GMP compliance has to be ensured by on-site audits of API manufacturing facilities in accordance with European legal provisions. Even GMP certificates provided by competent national authorities, for example from the Chinese State Food and Drug Administration (SFDA) or Indian regulatory authorities, are not sufficient enough to replace API audits.

Asian API manufacturers that supply their goods to regulated markets should therefore expect related GMP audits of their quality systems and manufacturing processes. These audits have to be performed under the responsibility of a Qualified Person or through contracted third-party auditors.

GMP regulations vary worldwide. The World

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Health Organization (WHO) has created a globally consistent basis for quality standards with the compendium "Quality Assurance of Pharmaceuticals." Chapter two describes the GMP requirements for "APIs (bulk drug substances)".

The US, Europe and Japan have adopted the "International Conference on Harmonisation (ICH) Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients," representing their own regulations for the manufacturing of APIs. These regulations substantiate and even extend the WHO requirements in several topics.

Within the European Union, the ICH Q7 regulations have been established as "EU GMP Guideline Part II," with (nearly) identical wordings. Other countries such as Canada, Australia and Singapore have also adopted the ICH regulations – the latter via the "Pharmaceutical Inspection Co-operation Scheme" (PIC/S).

Manufacturers should align their quality management systems and manufacturing processes to the requirements of ICH Q7.
(Source: blue inspection body)

Differing Standards

Most of Asia portrays a mixed image: whereas Japan and Singapore follow the ICH Q7 regulations, India and China – the major API manufacturing countries, have approved their own GMP regulations (although representatives of both countries were invited participants of ICH Q7 expert working groups). These GMP regulations simultaneously cover active pharmaceutical ingredients and medicinal products.

India has laid down its own GMP requirements in Schedule M of the "Drugs and Cosmetics Rules". In China, the rules from "GMP for Pharmaceutical Products" which have been issued by the SFDA are in force. Unlike the ICH Q7 which deals exclusively with APIs, the Chinese and Indian GMP regulations do not distinguish between GMP for medicinal products and GMP for APIs. Part 1-F of the Indian Schedule M is for API manufacturing while the SFDA GMP guideline has a corresponding appendix 4.

However, in both cases the number and complexity of rules are comparatively low. This may create problems for API manufacturers in these two countries. For instance, auditors from ICH may still find these manufacturers non-compliant even if the latter have adhered to their respective national GMP regulations.

Pharmaceutical companies that sell medicinal products within the ICH region have to comply with the valid ICH Q7 guideline, or the valid identical national regulations. GMP audits conducted in Asia by these companies must primarily be geared towards the legal requirements of the target market rather than those of the API supplying country.

As a general rule, such an audit will follow the structure and the requirements of the ICH guideline. The guideline is structured into 19 chapters (Table 1), with a number of audit topics. The differences between the effective GMP standards of the supplying countries and the receiving countries may therefore result in ambiguities and difficulties relating to GMP compliance.

From a fundamental standpoint, the differing structures between the CH Q7 and the Schedule M or the SFDA can cause difficulties in finding the required information. This opens up the possibility of misinterpretation by the auditor as the country or company specific GMP documents may not be presented in a way that he is familiar with.

This risk can be avoided by employing experienced auditors who are familiar with the regulatory guidelines in India and China. This means that the buyers of APIs have to ensure that the auditors are suitably qualified for the job.

Following the Rules

The differing requirements of the underly the GMP guidelines may also lead to real non-compliance. This for instance is the case, if topics defined within the ICH Q7 are not (or are only superficially) covered in national GMP guidelines.

Eg, topic 1.3 of the ICH Q7 (and topic 1.2 of the EU-GMP guideline, part II and topic 1.2 of the PIC/S GMP Guide for Medicinal Products part II) suggests the stage (starting point)

within the manufacturing process where GMP requirements need to be fulfilled for different kinds of API starting materials.

During the auditing of the process validation and manufacturing flow according to ICH standards, an auditor will emphasize on the adherence of the early stages of the manufacturing process to essential GMP requirements. With subsequent process steps up to the point of the purified, finished API, the auditor expects increasing GMP compliance.

The SFDA GMP rules on the other hand, are primarily focused on the final manufacturing steps. For the API manufacturing process, batch records are (only) required starting from the "refinement from crude" step (appendix 4, topic 10 of SFDA-GMP). Since regulations for the early manufacturing steps are not contained within the guideline, Chinese companies may be non-compliant according to ICH criteria – depending on their selection of the API starting material.

The subject of "change control" is covered in chapter 13 of the ICH Q7. Every change that is related to the production process that "may affect the production and control of the intermediate or API" has to be identified, documented, assessed and approved. This means that the API purchaser has to be informed about changes in the production process based on the ICH Q7 requirements.

However, local GMP regulations may not require API manufacturers to inform their purchasers about such changes. The Chinese SFDA GMP guideline does not explicitly dictate change control procedures. The Indian schedule M covers the changes in the manufacturing process in chapter 26.5. However, these changes are only regarded as a task for validation: "Significant changes to the manufacturing process, including any changes in equipment or materials that may affect product quality and/or the reproducibility of the process, shall be validated."

Changes in the manufacturing process may potentially lead to extremely altered properties of APIs, eg, the bioavailability and the resulting efficacy – the API exhibits identical chemistry properties with different eventual polymorphic forms. Therefore, unqualified and undocumented changes in the production process can result in serious consequences for the marketing authorization holder to the point of a termination of the manufacturing authorization.

Manufacturers from Asia should therefore align their quality management systems and manufacturing processes not only to their respective national standards but also to the requirements of ICH Q7. Otherwise, European and American companies cannot accept the APIs.

In most cases, the adaption of the quality systems is feasible. The topics are covered in the respective guidelines, but with different levels of complexity in the rules. The guidelines can be combined by implementing requirements from ICH as an extension to the national legislations.

'Black Sheep'

Intentional non-compliance can also occur and are usually due to economic reasons. Strict adherence to compliance implies a significant inflexibility to change, providing non-compliers with significant competitive advantages.

Compliant manufacturers are placed at a disadvantage because of these "black sheep": after incidents of intentional non-compliance, exported APIs from that country will be under the general suspicion of purchasers and regulatory authorities, leading to impeded market penetration. For instance, after contaminated Heparin from China led to more than 80 cases of death in the US, the affected pharmaceutical manufacturer Baxter started an immediate review of its China-based suppliers and their sources.

Additionally, companies have even added on their Bovine Spongiform Encephalopathy/ Transmissible Spongiform Encephalopathy (BSE/TSE) certificates, a phrase that states that their APIs and excipients are not manufactured in China.

Companies have even added on their Bovine Spongiform Encephalopathy/ Transmissible Spongiform Encephalopathy (BSE/TSE) certificates, a phrase that states that their APIs and excipients are not manufactured in China.

Table 1: Comparison of the chapters from relevant GMP guidelines in the US, Europe, India and China

ICH Q7 (USA) / EU GMP Guideline Part II (Europe)	21 CFR Part 211 (USA)	EU GMP Guideline Part I (Europe)	Schedule M (India)	SFDA GMP (China)
1. Introduction	A. General Provisions	1. Quality Management	1. General Requirements	1. General Provisions
2. Quality Management	B. Organization and Personnel	2. Personnel	2. Warehousing Area	2. Organization and Personnel
3. Personnel	C. Buildings and Facilities	3. Premise and Equipment	3. Production Area	3. Buildings and Facilities
4. Buildings & Facilities	D. Equipment	4. Documentation	4. Ancillary Areas	4. Equipment
5. Process Equipment	E. Control of Components and Drug Product Containers and Closures	5. Production	5. Quality Control Area	5. Materials
6. Documentation and Records	F. Production and Process Controls	6. Quality Control	6. Personnel	6. Hygiene and Sanitation
7. Material Management	G. Packaging and Labelling Control	7. Contract Manufacture and Analysis	7. Health, Clothing and Sanitation of Workers	7. Validation
8. Production and In-Process Controls	H. Holding and Distribution	8. Complaints and Product Recall	8. Manufacturing Operations and Controls	8. Documentation
9. Packaging and Identification Labelling of APIs and Intermediates	I. Laboratory Controls	9. Self Inspection	9. Sanitation in the Manufacturing Premises	9. Production Management
10. Storage and Distribution	J. Records and Reports		10. Raw Materials	10. Quality Management
11. Laboratory Controls	K. Returned and Salvaged Drug Products		11. Equipment	11. Product Distribution and Recall
12. Validation			12. Documentation and Records	12. Complaints and Adverse Reactions Report
13. Change Control			13. Labels and other Printed Materials	13. Self-Inspection
14. Rejection and Reuse of Material			14. Quality Assurance	14. Miscellaneous
15. Complaints and Recalls			15. Self Inspection and Quality Audit	
16. Contract Manufacturers (Including Laboratories)			16. Quality Control System	
17. Agents, Brokers, Traders, Distributors, Repackers, and Relabellers			17. Specification	
18. Specific Guidances for APIs Manufactured by Cell Cultures/Fermentation			18. Master Formula Records	
19. APIs for Use in Clinical Trials			19. Packing Records	
			20. Batch Packaging Records	
			21. Batch Processing Records	
			22. Standard Operating Procedures (SOPs) and Records	
			23. Reference Samples	
			24. Reprocessing and Recoveries	
			25. Distribution Records	
			26. Validation and Process Validation	
			27. Product Recalls	
			28. Complaints and Adverse Reactions	
			29. Site Master File	

As a consequence of such incidents, the legal or company specific compliance regulations are frequently and reflexively tightened. In the worst case scenario, such measures primarily serve to aggravate the economic conditions of honest market participants.

However, the problem cannot always be resolved with tighter regulations but with the continuous and professional auditing of the entire supply chain. GMP requirements need to be veritably fulfilled, starting with the manufacturer of the medicinal product to the related API trader, up to the manufacturer of the API.

While APIs and excipients have evolved into globally traded goods, GMP regulations have not kept pace with this development. Differences, particularly between the ICH region on one hand and China and India on the other, slow down the development of the market. In addition, these differences complicate the monitoring of successful GMP compliance. Achieving an international harmonization of the standards will take time.

Manufacturers of APIs that desire to take advantage of export opportunities should therefore not merely align their manufacturing processes according to the respective national regulations. Rather, they should consider the ICH Q7 requirements pertaining to their quality management system and documentation structure – and the additional expenditure is usually justified. Those that are not willing to adapt may end up facing closed doors to the American, Japanese or European markets. **PA**

Enquiry code: 094E01

Data Management: Information Integrity

The quality of data derived from clinical trials can determine the success or failure of a drug application.

Hanming Tu,
director, Clinical IT,
Octagon Research Solutions

Data quality is the life-blood of clinical trial data management. Poor data quality not only generates additional work for later clinical analyses but also carries the risk of eventually leading to the failure of a drug application. As more pharmaceuticals companies expand their clinical trials into Asian countries such as India and China, this issue is becoming a major concern to sponsors and regulatory agencies such as the US Food and Drug Administration (FDA).

What are the factors that one should consider when conducting trials in Asia? Is it possible to measure the quality of clinical data collected by a third party?

While there are many factors that can impact data quality, standards and training are considered the major ones when it comes to clinical trials in Asia. Although the language and cultural differences may be significant at the beginning, these can be minimized if standards are in place and adequate training is provided.

There are four steps that can lead to higher data quality: adopting a standard; training a team; measuring data quality with known criteria; and implementing a set of technologies to improve data quality.

Embracing a Common Standard

The key to data quality is in adopting a common standard, sticking to the standard practices and processes, and using technology to reduce human errors. Adopting a standard not only increases interoperability and efficiency, but also provides a foundation for data quality and its measurability.

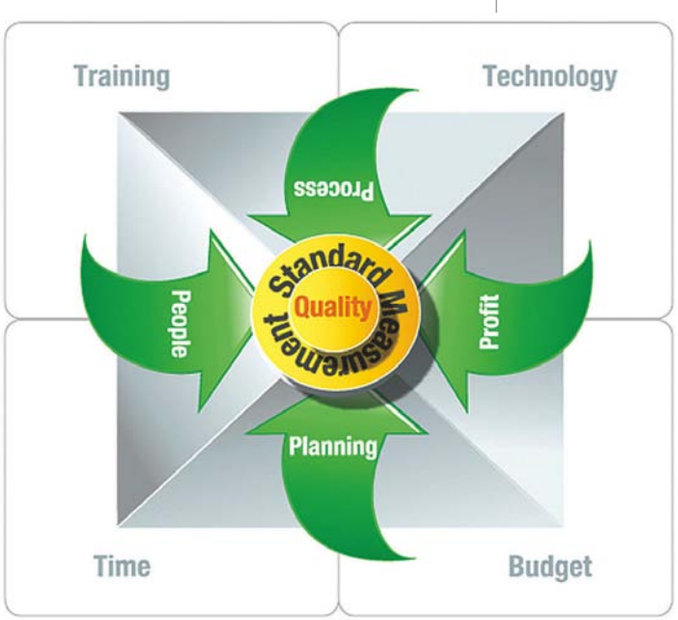


Figure 1: Conceptual Model for Achieving Data Quality. (Source: Octagon Research Solutions)

Pharmaceutical companies that are outsourcing work to Asia should first find out if a contract research organization (CRO) adheres to industry standard practices such as Good Clinical Practice (GCP), Good Laboratory Practice (GLP), and Good Manufacturing Practice (GMP). Secondly, it needs to check if the CRO has adopted a common data standard.

International Conference On Harmonization (ICH) has harmonized GCP. The FDA has recommended the Study Data Tabulation Model (SDTM) developed by the Clinical Data Interchange Standards Consortium (CDISC), as data standards for structure, terminology and code sets, in the Federal Register, Volume 71, No 237, December 11, 2006.

The lack of standards has become a bottleneck to utilizing and improving health informatics in China, as suggested in a study by the Institute for Health Information, Fourth Military Medical University. The main barriers presented in the process of standardization not only consists of financial, technical, cultural and language problems but also entails legal and ethical concerns.

One of the ways to minimize these problems and to ease concerns is to conduct standard-based training and interchanges. While the Chinese central and local governments have taken the initiative to try to improve on the lack of standards, the private sector seems to have been more proactive.

Team Building Through Training

There are two types of standards in clinical trials: ethical standards such as GCP and data standards such as the CDISC SDTM. GCP provides a unified standard in the conduct of clinical trials. It serves as an international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of trials that involve human subjects.

GCP has been practiced in the European Union (EU), Japan, the US, China, and other countries. Compliance with GCP provides the assurance that the data is reported, that the results are credible and accurate, and that the rights, safety and confidentiality of trial subjects are protected.

CDISC SDTM is a data submission standard and provides a stable structure for clinical studies and interoperability among systems. It has been adopted by companies in the US. In China, GCP has been exercised in certain projects but CDISC SDTM is still relatively new to Chinese investigators and clinical professionals.

The awareness and knowledge of standards come from education, training and self-motivated studies. GCP guidelines have been taught at US institutions such as the University of Southern California. The more immediate and effective way for learning the standards is via on-job training.

The 12th Healthcare Industry Forum held in Beijing in October 2008, carried the theme of "One World One Standard". The CDISC Coordinating Committee in China (C3C) was formed in the same month and hosted its first China Interchange in Shanghai. C3C directly advocates and promotes the CDISC standard adoption in China.

If the industry can adhere to the three "A"s: Advocating, Adopting and Advancing, the rapid adoption of the standard may be seen in the near future. The three 'A's must start with well-planned training.

There needs to be a common vision for developing safer and more effective drugs, efficiently and productively with common standards. The team has to consist of advocates, practitioners, developers, and supporters. As successfully demonstrated in the Comprehensive International Program for Research on AIDS (CIPRA) project, it is critical to have well-planned and implemented training and team building activities.

CIPRA is an initiative sponsored by the US National Institutes of Health (NIH) that provides long-term support for laboratory and clinical studies for HIV/AIDS prevention and treatment in developing regions. China CIPRA is conducted by the Chinese Center for Disease Control and Prevention (CDC) under the leadership of the Ministry of Health, together with other domestic and international scientists. It has a five-year grant of US$14.8 million and is composed of five inter-related projects and four cores. Core A encompasses administration and training.

Experts were hired from the Statistical Center for HIV/AIDS Research and Prevention (SCHARP), Westat, Premier Research, and NIH to give training to members from all the cores in the project. Many of the experts are native Chinese who have been working in the field for over a decade. The China CIPRA project also had advocating committees and working groups and was networked with other NIH projects in China.

The coordinated effort paid off. A study on the quality of international clinical studies in China was conducted by Jason Chang from the National Institute of Clinical Drug Studies at The Xijing Hospital, Fourth Military Medical University. The study concluded that GCP adherence between US and China for the project is similar in distribution pattern. Overall, the China CIPRA program was at least equivalent to US studies from an ICH/GCP perspective.

Measuring Data Quality Based on Criteria

When outsourcing clinical trials to a CRO, there needs to be credibility in the clinical data provided by the third party and in how it is collected and processed. It is nearly impossible to measure quality that one does not have control over and where there is no common standard. The "Specifications for Study Data Tabulation Model Validation Criteria for the Janus Operational Pilot" published by FDA in 2008 makes it possible to measure data quality through a commonly defined set of compliance checks – even if one does not have direct control over the data sets.

A data standard defines a target for data structure and content for systems and people. A well-designed system can become a tool for the production of standardized products.

In clinical trails, it is necessary to produce SDTM data sets. Since many trials were started before SDTM was developed by CDISC and recommended by FDA, efforts have been made by pharmaceutical companies to convert these legacy data sets into SDTM format.

Janus is a clinical trial data repository (data warehouse) standard that is sanctioned by the FDA. It provides a data model for clinical study data warehousing and enables an integrated review environment. FDA has conducted two pilot projects to load SDTM data sets into the data repository.

Many extracting, transforming and loading (ETL) tools have been developed and tuned to conduct data integration and standardization (DIS). Some companies including CROs in China are specialized in DIS and provide data conversion services. Since there are different ways to translate data, how does one know that the data is truly in SDTM format? And how can the quality of SDTM data sets be measured?

In the specifications for SDTM validation criteria published by FDA in January 2008, a set of 109 compliance checks have been defined, and these checks are classified into three levels of severity:

- **High:** The error is serious and will prevent the study data from being loaded successfully into the Janus repository.
- **Medium:** The error may impact the reviewability of the submission, but will not prevent the data from being loaded into the repository.
- **Low:** The error may or may not impact the reviewability or the integrity of the submission. It will not prevent the study data from being loaded into the Janus repository.

These compliance checks can be further categorized into three levels of validation:

- **Structure validation:** Checks the structure of the data sets including data type, column length, format, and presence of required variables.
- **Integrity validation:** Checks the relationship integrity of data sets including consistency (cross-column, cross-domain, external dictionary) and referential constraints.
- **Value validation:** Checks the value compliance in terms of limits (range, upper and lower bounds), code list, illegal values, and meta-data.

Based on these defined criteria, some companies have developed more extensive checks to validate SDTM compliance. Figure 2 shows the comparison list of the compliance checks between FDA and Octagon Research. This list is not exhaustive and the number of checks may increase in future. These checks provide a quantitative measurement for data quality against a targeted standard.

Category	Sub-category	Standard FDA Checks	Enhanced Checks
Structure	Format	6	53
	Presence	4	33
Integrity	Consistency	46	38
	Constraints	8	4
Value	Limit	10	2
	Metadata	8	45
	Defined value	27	42
Total		**109**	**217**

Figure 2: Compliance checks between FDA and Octagon Research

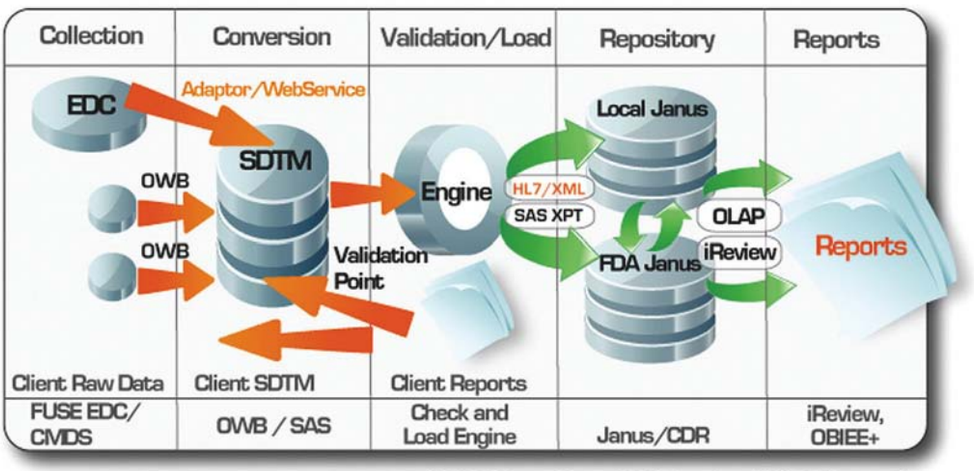
Leveraging on Technology to Improve Data Quality

Once the criteria have been clearly defined, utilizing ETL and database technologies can help to streamline the process of data conversion and validation. The model of the extended validation engine in the ETL process involves the following:

- Adding a validation process (compliance check) between transformation and loading, where the compliance check is to ensure conformance to both the data model and the business rules.
- Maping CDISC SDTM domains and variables with Janus tables and columns.
- Building the meta-database, including a code list for all the controlled variables.
- Defining dimensions, hierarchies and cubes for Online Analytical Processing (OLAP).

Figure 3 shows the implementation model for the validation engine in the entire clinical data management process. Clinical data is collected through a regular clinical data

Clinical Trials



Implementation model for the validation engine in the entire clinical data management process. (Source: Octagon Research Solutions)

management system (CDMS) or electronic data capture (EDC) system. The data sets are converted to SDTM using an ETL tool such as Oracle Warehouse Builder (OWB), or exported to SDTM format if the EDC is SDTM compliant.

The SDTM data sets are put through a checkpoint (validation engine) and uploaded into Janus data warehouse if they pass the data quality validation. Once all the data sets from different companies or from different therapeutic indications are loaded into this single repository, users or regulators will be able to review them in the same environment, possibly with the same set of tools.

Many data conversion projects in China or other Asia countries are conducted by clinical programmers using a computer programming language such as SAS, PL/SQL, Java, or Perl. The resulting data quality depends on the programmer's skill and the enforcement of standard operating procedures for quality control by the CRO.

Implementing an industry strength ETL tool such as OWB will allow a company to enjoy the benefits of:

- **Hiring non-programmers (who cost less);**
- **An audited environment;**
- **Built-in security;**
- **Consistency among all the users;**
- **Ease of management and support.**

However, as it is typically expensive to deploy and maintain such systems, few CROs in Asia can afford them.

Ideally, the data that is collected in a system should be compliant to the SDTM standard. All data issues should be resolved before the data sets are pushed downstream for processing. Some EDC systems are already SDTM aware or compliant, for example, PhaseForward's InForm EDC, Octagon Research's ViewPoint Fuse, etc.

It is only beneficial to use an EDC system at the commencement of a clinical trial. The deployment of such systems has been slow in the past decade. More clinical data sets will need to be converted to SDTM and to be put through the validation engine to encourage more clinical studies to be conducted with EDC systems.

Pumping data through a validation engine to validate clinical data sets is the final step that one must take before submitting the data sets to the FDA and committing the user fee for the drug application.

Once FDA improves on its infrastructure and has the capability to load and store all clinical data in the Janus data warehouse, even the data coming from a SDTM compliant system may have to go through a validation process before it gets loaded into the clinical repository.

While it is important to complete projects on time and within budget, it is also necessary to ensure quality as well. With commonly recognized standards, it is possible to achieve data quality through training, defined measures, and technologies.

The goal is to timely develop safer drugs and to enhance public health. With the collective effort of the life science industry, it is possible to build a standards-based and process-centric platform that integrates technologies, processes, and people to achieve higher data quality across the world. **PA**

Streamlining the Clinical Trials Lifecycle through Electronic Initiatives

Electronic data capture and reporting technology holds the key to improving the efficiency of clinical trials and the safety of patients.

Dr Michael McKelvey,
CEO,
ERT

Electronic initiatives such as electronic data capture (EDC) and electronic patient reported outcomes (ePRO) are revolutionizing the conduct of clinical trials in the pharmaceutical industry. Besides assisting in the retention and compliance of clinical trial subjects, these initiatives help to develop a more efficient and reliable means of data collection and analysis.

The increased use of such technology is encouraging a more centralized way of working. In turn, this centralized approach means that standardized data and performance metrics can be gathered and analyzed to drive further improvements in the efficiency and the validity of clinical trials.

Pharmaceutical companies are keen to reduce the time required to get a new drug to market in the most efficient and cost-effective way, in order to maximize profits and ensure patient safety. Costs have to be mapped out before the start of a trial, which means that it is important to generate accurate data. Inaccuracies in data capture mean that the results may not be reliable and repeat testing is required as a consequence.

Repeated testing is detrimental to a trial as it incurs further expenses. In addition, manual methods have a further impact on budgets as the former require a substantial staff headcount, mainly due to the number of labor-intensive processes involved.

Data Capture

As the financial commitment that is required to bring drug products to market continues to rise, so too does the need to generate better answers about safety and efficacy.

Traditional methods of data capture in clinical trials are time consuming and can be subject to inaccuracies in both the recording and the analysis of results. These methods rely on face-to-face interviews and manual data collection and interpretation. Human errors are common during the transferring of data. Some clinical trial subjects may find face-to-face methods uncomfortable and statistics reveal that they can be less truthful in such situations.

A centralized approach means that standardized data and performance metrics can be gathered and analyzed to drive further improvements in the efficiency and the validity of clinical trials. (Source: ERT)

In order to meet the demand for quicker and more cost-effective ways of conducting clinical trials, the industry is moving away from manual methods of data capture and interpretation, in favor of electronic methods.

The power of modern computers allows tasks and entire processes to be completed, while providing the additional benefits of improved methodologies, higher speeds and lower costs. This transition from traditional methods to electronic data collection, analysis and reporting is helping to revolutionize clinical trials.

EDC is one approach which provides the ability to efficiently and effectively collect, interpret and distribute quality data. This method is crucial for facilitating decision making and providing the ability to bring safe drugs to market faster. These systems typically utilize digital equipment that provide a graphical user interface component for data

entry. Such systems also offer a validation component to check user data, and tools for reporting data analyses.

Data captured via EDC is stored in a central CDMS (Clinical Data Management System) and is immediately available for monitoring and source-document verification.

Web-based systems allow investigators to log their findings directly into a centralized database to deliver accurate data in real-time. This data may then be analyzed to review the progress of clinical trials, to support trial adaptation and to reduce the cost of providing statisticians with study information.

With the increasing acceptance of EDC by the pharmaceutical industry, the focus is starting to move towards the further streamlining of processes. This is to enable faster and more cost-efficient clinical trials. In order to achieve this, a pre-configured EDC solution is needed with prior or advanced systems validation. This can only be achieved through the gathering of key performance indicators or via a standard set of performance metrics.

Standard performance metrics can identify potential problems earlier in the clinical trials process. These issues can then be addressed proactively, allowing costs savings to be achieved by avoiding the need for repeat testing. The use of selected metrics can aid the forecasting of future trends as well as provide an indicator of the progress of a clinical trial. The reuse of validated metrics on future projects provides savings that help to offset the initial startup costs of an EDC system.

Through a centralized interactive data warehouse, it is possible for regulatory bodies to review the raw data analysis points and to perform re-measurements to confirm the accuracy and consistency of a central core laboratory methodology.

Electronic Patient Reporting

Clinical trials can be delayed due to slow enrollment, problems with paper documentation and the inability to monitor sensitive patient data – costing sponsors several million dollars. Conventional methods of patient compliance and retention are still widely used, but have a poor success rate as they require the patient to take the initiative.

The power of modern computers allows tasks and entire processes to be completed, while providing improved methodologies, higher speeds and lower costs. (Source: ERT)

Electronic patient reported outcomes (ePRO) solutions are available, which enable electronic diaries to be derived directly from the patients – a process that is critical to proving the efficacy of a potential new compound and its effects on patient safety.

While the use of Personal Digital Assistants (PDA) and other handheld computer solutions such as ePRO tools are on the increase, these can involve a major commitment in capital, time and resources. Phone-based, voice-response solutions are less expensive and are more readily available.

Interactive Voice Response (IVR) is an interactive technology that allows a computer to detect voice and telephone keypad inputs. IVR tools have been designed and optimized to help facilitate the collection of clinically valid and sensitive data directly from participating patients. The use of both cell phone technology and IVR eliminates the need for face-to-face interviews.

In the early stages of a trial, electronic tools can help to ensure the enlistment of suitable clinical trial subjects and that direct channels of communication with the patient are always open. Phone-based technology can be deployed to support existing recruitment methods such as physician referral and advertising in hospitals, clinics and universities.

Advertising campaigns can direct potential clinical trial subjects to call a toll-free number and complete an automated recruitment questionnaire, for the identification of suitable candidates. Such candidates are then referred to the nearest study site for full registration. Unlike traditional methods, ePRO recruitment techniques deliver instant information on the success of the recruitment process. Response rates typically increase by around 20 percent when using electronic methods.

Ensuring Patient Compliance

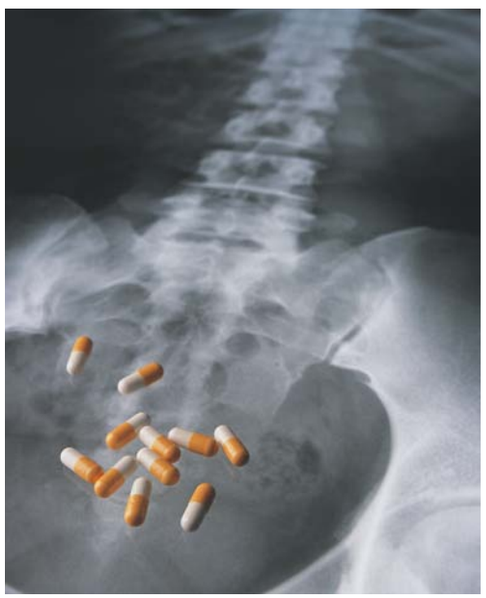
Once the trial subjects have been selected, the next challenge for companies is to ensure that patients adhere to the clinical trial conditions (ie, taking the correct medication dosage). Patient non-compliance costs the pharmaceutical industry several billion dollars each year. Reminder letters or and/or telephone calls account for a portion of these costs.

The issue of patient non-compliance is being addressed with the use of electronic technology to open up direct channels of communication with clinical trial subjects. Automatic reminders can be sent via cell phone to a subject to help ensure that the latter complies with the requirements of the study. The messages can be tailored to each individual to contain information such as medication dosage and administration. A message delivery report system can also be implemented to determine if the messages have been received.

Statistics show that on the average, 25 percent of subjects drop out of trials before completing the full study. Retaining patients may require ongoing support and motivation throughout the trial. It is important to keep the patients engaged and to ensure that their well-being is maintained.

Traditionally, patients were given detailed information on medication and the latter's possible side-effects at the start of a clinical trial. However, studies have shown that a more effective method is to keep patients constantly updated on the progress of a trial – which can be difficult using traditional methods.

ePRO can be adapted to cope with the changing regulatory environment within the clinical trials arena. Concerns pertaining to suicidal behaviors in patients during clinical trials, is an example of how the tools can be adapted to assist companies in maintaining regulatory compliance and patient safety monitoring.



Suicidality Monitoring – Boosting Safety

The need for the prospective monitoring of suicidality in clinical trials is increasing. Drugs can influence the types of chemicals that enter the brain which affect emotions, thoughts and behaviors. It has been shown that even medicines that are used to treat acne, asthma and insomnia may cause suicidal tendencies. In response to the possible psychiatric side effects of such medicines, the US Food and Drug Administration (FDA) has commissioned researchers at Columbia University to develop the Columbia-Suicide Severity Rating Scale (C-SSRS) – a semi-structured clinical interview that is to be conducted with subjects during trials.

However, clinician-administered assessments are known to be plagued by rater variability, which can be even greater when clinicians have minimal mental health training. Even after extensive training, rater skills deteriorate over time. Such variability decreases the reliability and accuracy of these assessments and ultimately their value in detecting suicidality indicators.

Given the growing range of medications being evaluated for causing suicidal tendencies, there is a need to develop a fully-structured, procedurally reliable and replicable process for obtaining SSRS data. Studies have demonstrated that patients tend to disclose more suicidal thoughts and behaviors in non-human computer interviews, than to clinicians.

ePRO tools have advantages in monitoring suicidal behaviour, compared to both face-to-face and paper-based data collection methods. The tools provide confidentiality, since the information is collected directly from patients. Direct patient-computer interviews can be also be conducted via text-based assessments or by IVR technology using telephones as an alternative to PC-based technology.

Automated IVR-SSRS programs can reliably and accurately identify changes in suicidality signals, which in turn increase patient safety. Typically, these automated systems are backed by a response system that allows swift reaction to suicidality concerns. Certain patient-reported answers trigger alerts to the trial site via a pair of call centers that maintain contact until investigators are alerted and the patient is successfully contacted.

In clinical trials, patient responses are obtained, checked for validity and the data is stored in an electronic database. IVR provides the opportunity to ask highly sensitive questions and receive replies in a non-judgmental environment. Using computers and phones to automate suicidality assessments reduces the risk of false negatives and maximizes signal sensitivity to evaluate the true effects of new compounds and drugs.

Costs have to be mapped out before the start of a clinical trial, which means that it is important to generate accurate data. (Source: ERT)

Maximizing Resources with Technology

The ability to save both time and money throughout the lifecycle of a clinical trial is a key benefit in today's challenging pharmaceutical market. More companies are realizing the benefits of electronic tools as a means of speeding up both data capture and analysis.

When ePRO tools are deployed effectively, they eliminate issues that are often encountered through the use of traditional methods. Besides assisting in the recruitment, retention and compliance of clinical trials subjects, direct channels of communication with subjects can be maintained. This allows patients to instantly record information about the effects of a drug through the use of web or phone-based electronic diaries. It eliminates the need for face-to-face meetings and allows patient responses to be monitored in real time by sponsors, thereby ensuring patient safety.

One of the keys to the future success of EDC technology lies in its ability to support the reuse of software and data components for successive studies, without the need for significant programming to accommodate study differences. The technology presents an opportunity to reuse validated workflows and process tools from previous trials, via a centralized database. This ability means that data managers can better spend their time on performing analytics instead of generating queries. **PA**

Enquiry code: 094E03

Supply Chain Management: Combating Counterfeits

Faced with the threat of counterfeit drugs, the global pharmaceutical supply chain needs to respond with increased collaboration and more effective security mechanisms.

John Paul,
MD,
iCognitive

The pharmaceuticals drug supply chain from the manufacturer to the pharmacy usually includes several intermediaries such as wholesalers and distributors. This opens the supply chain to the risk of counterfeit drugs and encourages parallel trade, leading to lost sales for the manufacturer. The problem is more prevalent in developing countries with weak regulatory regimes. It is estimated that counterfeit drugs accounted for about 10 percent of the global pharmaceutical market in 2007.

Major Sources

A large proportion of the world's counterfeit medicines originate in Asia, where the production of substandard and fake drugs is a vast and underreported problem. The US Food and Drug Administration (FDA) has estimated that in parts of Asia, fake drugs account for more than 50 percent of medicinal sales and kill several thousand people every year.

China is a production center of such drugs. In 2005, Chinese local industry and commerce administration departments uncovered a number of cases involving the production and selling of fake medicine. According to the survey studying 6,500 companies in twelve provinces across China, 33 business licenses were revoked and 67,000 boxes of fake medicine were seized.

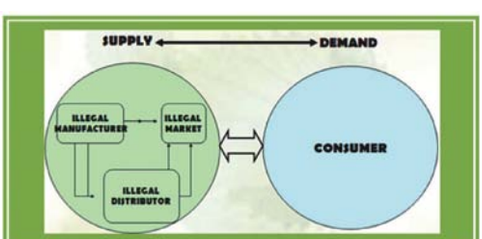


Figure 1: Supply chain of counterfeit drugs (Source: National Agency of Drug and Food Control, the Republic of Indonesia)

According to World Health Organization (WHO) statistics, India accounts for one-third of counterfeit drugs produced worldwide. In Australia, 18 companies are facing legal actions for advertising false health-benefit products on the web, following a worldwide internet sweep by the Australian Competition and Consumer Commission in 2006, for false claims about health products.

Counterfeit drugs have been closely related to the global public health problem causing death, disability and injury. Factors leading to counterfeiting can be summarized in Figure 1. The drugs are locally manufactured by illegal manufacturers or have been illegally imported, and are subsequently distributed to illegal markets before reaching end consumers.

Therefore, pharmaceutical production and distribution are two main areas where national drug regulatory authorities need to focus their attention. Nevertheless, governments are often reluctant to publicize problems with the quality of the drug supply in their respective countries – reflected in the lack of action taken.

There are also other factors that contribute to the proliferation of counterfeiting. Firstly, the continuous deterioration of economic conditions makes pharmaceutical products unaffordable to certain consumers. Secondly, counterfeiting is worsened by the lack of compliance to regulations that prohibit the selling of drugs outside pharmacies and authorized outlets. For instance, the violation of regulations that require products to be sold with a prescription contributes to the proliferation of counterfeit drugs.

Third, the imposition of mild or inadequate penalties, the price differences in pharmaceutical products and the lack of public awareness all open the door to counterfeit products. Access to medicines through the internet has also increased cross-border trade and has presented another opportunity for counterfeits.

The Toxic Pipeline

A series of cases have been reported where poisonous pharmaceutical ingredients have flowed into the global market through traders and middlemen that formed a supply chain stretching from small factories in rural China to consumers around the world.

One such example involved the syrupy poison diethylene glycol which led to several hundred deaths in Panama. Forty-six barrels of the toxic syrup arrived via a poison pipeline stretching halfway around the world. Through shipping records and interviews with government officials, The New York Times traced this pipeline from the Panamanian port of Colón, back through trading companies in Barcelona, Spain, and Beijing, to its beginning near the Yangtze Delta.

The counterfeit glycerin passed through three trading companies on three continents, yet not one of them tested the syrup to confirm what was stated on the label. Along the way, a certificate falsely attesting to the purity of the shipment was repeatedly altered, eliminating the name of the manufacturer and previous owner. As a result, traders bought the syrup without knowing where it came from, or who manufactured it.

There are however, potential supply chain oriented solutions to deal with counterfeit drugs:

• National Coordination

In order to contain the global counterfeiting scourge, it is necessary to address those dynamics which encourage the manufacture and supply of counterfeit medicines. This requires both national and regional joint efforts, as well as the support from international organizations such as WHO.

• Strategic Collaboration

For major suspected drug markets within a region, a joint effort of the respective National Agency of Drug and Food Control (NADFC) and law enforcement authorities should strengthen the inspection and investigation on targeted operations to ensure compliance to FDA cGMP (current Good Manufacturing Practice). Key players in the pharmaceutical supply chain, such as manufacturers or importers, wholesalers and retailers, as well as health professionals, also hold critical roles and responsibilities.

Manufacturers or importers should develop measures such as the introduction of security systems including the use of security tags, securing stocks of medicines and packaging materials, regularly surveying drug distribution channels, and promoting drugs in a way that results in demands that can be met by their own supply system.

Wholesalers and retailers should purchase drugs from legitimate sources, employing suitably qualified persons – preferably pharmacists, and report to NADFC any suspected counterfeit drugs in the national distribution channels.

Performance Attribute	Level 1 metric
Supply Chain Reliability	Perfect Order Fulfillment
Supply Chain Responsiveness	Order Fulfillment Cycle Time
Supply Chain Flexibility	Upside Supply Chain Flexibility
	Upside Supply Chain Adaptability
	Downside Supply Chain Adaptability
Supply Chain Costs	Supply Chain Management Cost
	Cost of Goods Sold
Supply Chain Asset Management	Cash-to-Cash Cycle Time
	Return on Supply Chain Fixed Assets
	Return on Working Capital

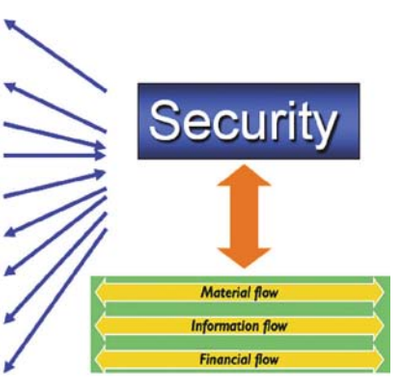


Figure 2: Security Parameters Inherited in SCOR Level 1 Performance Metrics.
(Source: Security Parameters in International Supply Chain Methodology, Prof John Paul)

Leveraging on Technology

Several technologies have been adopted to combat the drug counterfeit problem. Radio Frequency Identification (RFID) uses electronic devices to track and identify pharmaceutical products by assigning individual serial numbers to the containers holding each product. The FDA

is working towards an Electronic pedigree (ePedigree) system to track drugs from factory to pharmacy.

This technology may prevent the diversion or counterfeiting of drugs by allowing wholesalers and pharmacists to determine the identity and dosage of individual products. Moreover, techniques such as Raman spectroscopy and Energy Dispersive X-Ray Diffraction (EDXRD) can be used to discover counterfeit drugs that are inside their packaging.

According to the Singapore National RFID Centre, label manufacturing and RFID converting technology has reached another frontier with the development of an RFID Label Converting machine. The machine targets typical applications in supply chain, consumer packaging, pharmaceuticals and baggage tracking. It provides a low cost method of converting a RFID tag for embedding into a paper label.

While technology can be used to identify and track authentic products, the larger threat to the pharmaceutical supply chain is the secondary market – small, loosely regulated wholesalers and suppliers whose products occasionally enter the mass market. These drugs are sometimes used to fill in the gaps during an inventory shortage and can be priced significantly lower.

Many counterfeit drugs have come through these distributors, which are typically state-licensed entities that are supposed have been inspected by the pharmacy board. Nevertheless, a proper screening and business relationship building process is usually lacking between these distributors and their respective manufacturers, which has led to questions being raised about product legitimacy.

Verification Through Screening

In the white paper "The New Step by Step Approach to Client Screening", Rupert de Ruig, MD of Dow Jones Risk & Compliance, examines how anti-money laundering and compliance officers and industry vendors must embrace a "one step at a time" philosophy as a practical solution to the challenges posed by commercial watch list screening. Anti-money laundering (AML) screening involves the systematic examination of existing and prospective client identity details against a commercial database of persons and entities.

This paper proposes how a risk-based single step approach can be the key to managing costs whilst enhancing effectiveness. By applying this approach to their client and transaction screening, regulated firms can reduce costs while increasing the effectiveness of the process.

In a similar manner, targeted risk-based screening can be applied to and beneficial in dealing with the counterfeit drug problem. The case on McKesson illustrates that a secure and healthy relationship between pharmaceutical wholesalers and manufacturers is critical. Since 2001, the company only buys drugs directly from pharmaceutical manufacturers. Of the several hundred million products that go through its system every day, less than one percent is from the secondary market.

The company has an active business relationship with 10 alternative-source vendors. It initiates a rigorous due diligence process, including background and security checks as well as site visits, before it will purchase products from these vendors.

In the face of the drug counterfeit problem in the global supply chain, it may be feasible to adopt Supply Chain Management (SCM) tools and best practices, such as the Supply-Chain Operations Reference (SCOR) model. The model allows an organization to manage its supply chain with integrated planning and lean management. This is to improve global operations by reducing waste vertically and horizontally throughout the supply network.

This model allows companies to measure the supply chain network horizontally, from suppliers' suppliers to customers' customers. It also allows vertical measurement with cascading techniques from organizational strategic level to implementation level at the bottom.

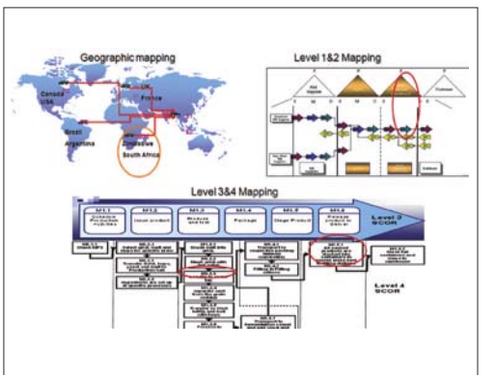


Figure 3: Top-down systematic mapping. (Source: Security Parameters in International Supply Chain Methodology, Prof John Paul)

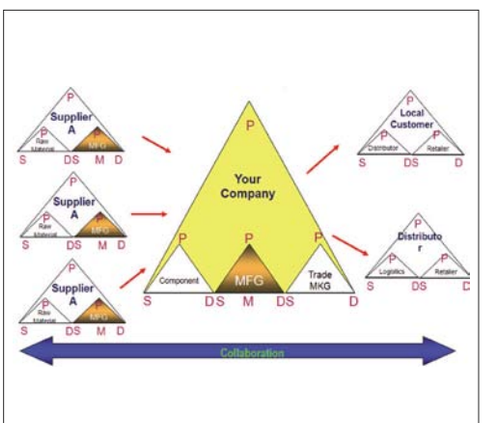


Figure 4 Foundation for security collaboration. (Source: Security Parameters in International Supply Chain Methodology, Prof John Paul)

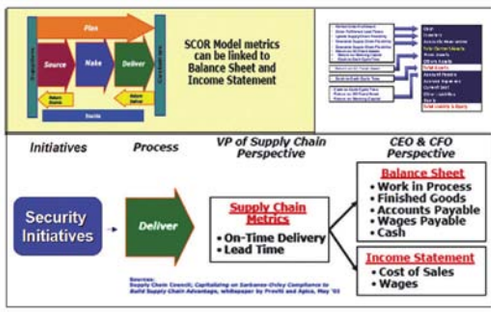


Figure 5: Link security initiatives with bottom-line operations. (Source: Security Parameters in International Supply Chain Methodology, Prof John Paul)

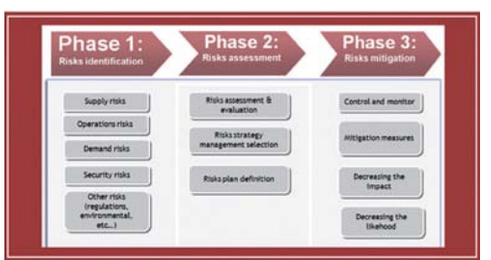


Figure 6: Three-phase approach for supply chain risk management. (Source: Supply Chain Operations Reference Model Version 9.0, Supply Chain Council)

Figure 7: Identification of different types of risks along the supply chain. (Source: Supply Chain Operations Reference Model Version 9.0, Supply Chain Council)

Supporting Decision Making

SCOR is structured around five core processes of Plan, Source, Make, Delivery and Return. The model outlines the process for establishing, maintaining, and enforcing decision support criteria for supply chain planning which then translates into rules for conducting business, ie, developing and maintaining customer and channel performance standards of an entire supply chain. For example, determining service levels based on requirements by supply chain stakeholders/trading partners or particular regulations in that industry.

Business rules align Plan process policies with business strategy, goals, and objectives of the organization, making sure that they are compliant with related regulations, such as FDA cGMP for pharmaceutical products.

The model also specifies metrics and best practices to monitor and maximize the efficiency of such enabler processes. For example, it measures the cost and cycle time required to manage business rules for Plan processes and suggests best practices to integrate business and supply-chain planning processes.

Security and Collaboration

Figure 2 presents the five performance attributes with ten metrics at Level 1 of the model. Security is closely associated with each metric. As an enabler, security contains good practices that protect continuity of supply, increase supply chain reliability, and protect assets from miscellaneous risk.

However, if its integration is not designed and implemented efficiently, it may result in the delay of supply and an increase of lead time and cost. Hence, it is important to adopt well-established supply chain management methodologies to help in systematic security design.

The model facilitates the design and deployment of security management through top-down mappings on activities at all levels of a supply chain. As illustrated in Figure 3, it starts with Geographic Mapping, Level 1 & 2 Mapping at the strategic and configuration level, followed by Level 3 & 4 Mapping at process element and implementation levels. Through systematic mappings, the model aids in:

- Identification of vulnerable locations or processes or elements
- Better integration between supply chain processes and security processes
- Ease of responsibility and resource allocation

In addition, the model provides the foundation and tool for secure collaboration as it sets a common language for communication across companies and industries and requests clear understanding of processes from suppliers and customers (Figure 4). Having laid out the strategic measures to integrate security into supply chain performance, the model also links security initiatives with bottom line operations at the shop floor (Figure 5).

Supply Chain Risk Management (SCRM) is defined as the systematic identification, assessment and mitigation of potential disruptions in supply chain networks with the objective to reduce their negative impact on the supply chain network's performance. Figure 6 illustrates a three-phase approach for SCRM, containing steps to identify, assess and mitigate potential risks.

Risk Management

In general, different kinds of risks in the supply chain network can be categorized in Figure 7. Multiple risks may be embedded in the core processes Source, Make and Deliver, as well as global risks caused by terrorism or economic crises, etc.

SCOR recommends tools such as Geographic Mapping to identify the geographical location for the origin of risks and potential methods to investigate the root causes. With respect to risk assessment, companies are usually concerned about the frequency of risk occurrence, the impact of risks, and where the greatest risk may exist. The assessment grid

shown in Figure 8 is a helpful tool for decision making on such issues. The vertical axis of the grid measures the probability that the event will occur, while the horizontal axis measures the consequences on the organization if the event occurs.

To estimate the frequency of the event occurring, historical data may be used if available. Alternatively an organization can use a subjective likelihood, or degree of belief based on the opinions of experts. Impact can be measured directly, for example in terms of dollars; or on a scale from zero to one with zero representing little consequence, 0.5 indicating moderate consequence, and one signifying a negative consequence. Methods for measuring impact include "what-if" simulations, financial models, opinions from a team of experts, or other metrics.

The model recommends that risks should first be controlled and monitored, and followed up with mitigation plans to decrease the likelihood or impact of the risks. In addition to strategic recommendations, the model also proposes statistical analysis for risk monitoring. For example, box plots are effective in monitoring suppliers' risks, by plotting delivery performance of various suppliers, as displayed in Figure 9.

Similar to the evaluation and implementation of other SCOR processes, performance metrics and best practices have been established for SCRM. Metrics are designed to measure the probability, physical and monetary impact of risk events, the total cost of executing the mitigation plan, as well as the degree of residual risk that might exist after mitigation. Two examples of best practices for SCRM are:

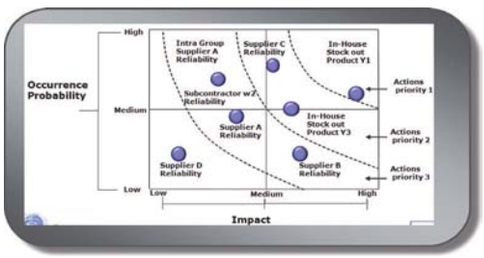


Figure 8: Occurrence probability-impact grid for supply chain risk assessment. (Source: Supply Chain Operations Reference Model Version 9.0, Supply Chain Council)

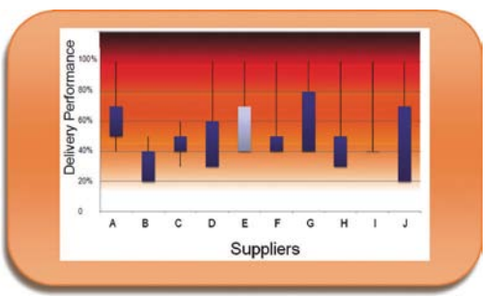


Figure 9: An example of using box plot for supplier risk monitoring. (Source: Supply Chain Operations Reference Model Version 9.0, Supply Chain Council)

• Configuring the supply chain network

This practice guides the design of the supply chain network based on a comprehensive risk evaluation pertaining to factors such as node locations, transportation routes, etc. This practice relies on the information collected through risk identification and risk assessment processes to determine nodes that are at a high risk due to the location of the node. Location specific risks can include tactical strike risks, single point of failure risks, etc. In regard to counterfeit drugs, a thorough understanding of manufacturing sites and distribution paths of its supply chain network is vital to address the problem at an international level.

• Configuring supply chain information

The second practice involves information sharing with partners as well as internal locations. This helps all parties to be quickly informed of a real or potential problem and to respond appropriately to minimize the impact. Indeed, information and communication are of paramount importance in combating counterfeit drugs. As shown in the Panama case, the toxic syrup traveled across borders with several nations and cities involved. Although the lack of reliable information was the root cause of this case, the tragedy should also be attributed to insufficient information being disseminated to educate consumers and health professionals.

FDA plans to increase dissemination of the public service announcements (PSAs) and counterfeit drug messages through updates and postings of relevant information on the counterfeit drug webpage. The organization will continue to work with the National Health Council (NHC) and pharmaceutical organizations to finalize educational messages and develop a dissemination strategy for pharmacists as well as the general public.

Effectiveness in combating counterfeit medicine requires collaboration and coordination among stakeholders in each country, as well as between member countries and partner organizations.

At the same time, efficient tools for global supply chain management and monitoring are needed. The SCOR model provides a systematic framework, detailed guidelines on procedures, performance measurements and best practices to manage the global pharmaceutical supply chains. It aims to achieve end-to-end visibility and mitigate potential risks within the supply network. **PA**

Enquiry code: 094E04

API Manufacturing: Product Safety

Agencies in Europe and the US are stepping up their efforts in Asia to ensure quality and safety in pharmaceuticals products.

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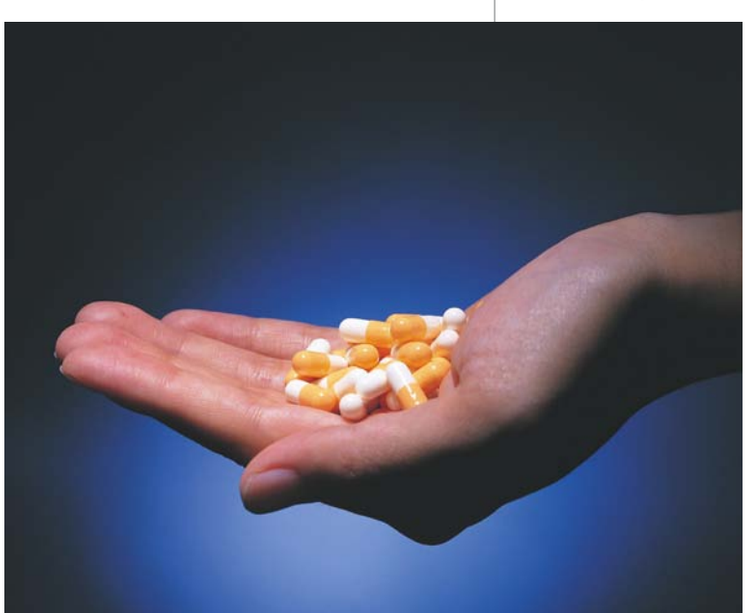
The Active Pharmaceutical Ingredients (API) manufacturing industry is becoming more complex with countries in Asia moving aggressively to supply ingredients to regulated markets such as US and Europe.

While the US and European pharmaceutical industries are experiencing little or no growth in this market segment, Asian producers are seeing high growth rates, both from domestic demand and export sales. According to statistics, Chinese API producers generated estimated revenues of US$4.4 billion in 2005 and are projected to achieve sales of US$9.9 billion in 2010. Indian API producers accounted for about US$2 billion in sales in 2005. This figure is projected to grow to US$4.8 billion in 2010.

Chinese pharmaceutical companies are primarily oriented towards supplying their own domestic market and tend to place less emphasis on external Good Manufacturing Practice (GMP) compliance. Indian API manufacturers, on the other hand, are focused on export sales to highly regulated global markets. These manufacturers have developed considerable expertise in complying with global GMPs and supplying documentation to foreign regulatory agencies.



Asian API and drug manufacturers can achieve compliance and avoid production stoppages and recalls by following the guidance issued by regulatory agencies.

With the rising costs of pharmaceutical products and the emergence of low-cost competitors, manufacturing efficiency is becoming more important to Asian API manufacturers. The latter are looking toward regulated markets for growth – which means complying to GMP. The issue of cost and safety for the producers of API manufacturing equipment is also a significant driver for growth in this industry.

Approximately, 80 percent of the APIs used in the US and the European Union (EU) to manufacture finished pharmaceutical products come from Asia, with China and India accounting for much of the supply. An increasing number of manufacturing facilities for APIs have relocated to Asia. However, foreign manufacturers have concerns about producing certain proprietary drug products in Asia, due to weak intellectual property protection laws.

Some Asian countries make it difficult for small foreign support companies that provide validation, quality, laboratory and technical consultant services, to establish local businesses and to enter the market. As a result, many larger foreign and local API and pharmaceutical companies have to import these knowledge-based services at a higher cost than it could have been provided for local businesses.

Quality and Safety Issues

Asian API and drug manufacturers can achieve regulatory compliance and avoid production stoppages and recalls by following the guidance issued by the US Food and Drug Administration (US FDA) and the European regulatory agencies. In addition, manufacturers must also understand that education and training are a key business investment that will produce safe and effective products in the long run.

International regulatory bodies have published various types of guidance. For example, Annex 18 – EU Good Manufacturing Practices Active Pharmaceutical Ingredients (APIs); Pharmaceutical GMPs for the 21st Century – A Risk-Based Approach Final Report; Quality Systems Approaches to Pharmaceutical Current Good Manufacturing Practice (GMP) Regulations.

The US FDA has also published a process validation guidance document titled, "Process Validation: General Principles and Practices".

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

The documents are not intended to create requirements for pharmaceutical manufacturing that go beyond those established in the current regulations, nor are they intended as a guide for the conduct of US FDA and EU inspections.

Japan is currently the leader in understanding the regulatory and compliance requirements that are needed to produce a high quality pharmaceutical product.

India's pharmaceuticals industry has been one of the fastest growing sectors in its economy. The country is now one of the most important healthcare markets in the world, having its own domestic market as well as a pool of clients for exports. Moreover, India is considered to be ahead of China in terms of its control of quality in pharmaceuticals manufacturing.

Growth and Regulatory Concerns

Where the US and EU manufacturers used to supply 90 percent of global API demand 20 years ago, they are now producing less than 20 percent. At the same time, while generic medicines accounted for less than five percent 20 years ago, they now make up for over 50 percent, with much of the API coming from Asia.

Figure 1 shows the cost structure differential between European/US manufacturers and manufacturers in India and China. Key to numerical superscripts:

(1) Includes cost of goods sold excluding cost of raw materials.

(2) Assessment of direct personnel cost reduction from approximately €60 to €6 total salary dollars (tsd)/ Full-Time Equivalent (FTE) where1€=$1.25. Indirect personnel has a cost reduction factor of 2.

(3) Assessment of direct personnel cost reduction from approximately €6 to €3 tsd/FTE.

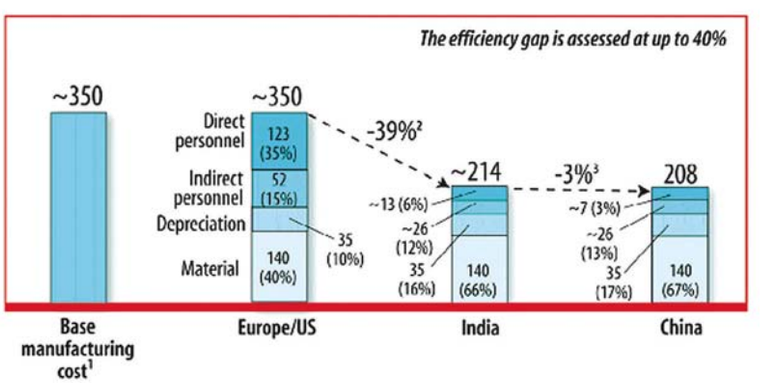


Figure 1: Assessment of API manufacturing costs by region in million Euros, basis 2004. (Source: Pharmaceutical Technology, 2005)

Consumers take it for granted that the medicines they buy are manufactured to the highest standards, and expect the regulatory authorities to ensure that this is enforced. In reality, there is a likelihood that the drugs on the shelves of European and US pharmacies may contain APIs that were made in Asian manufacturing facilities that have never been inspected.

Compliance with GMP regulations means that each of the batches of an API are of consistently good quality throughout the entire manufacturing process. Any changes to the process can only be implemented after their impact on quality has been assessed, and process change records must be kept so that all actions can be traced, if necessary. However, without a proper understanding of GMPs, the consistency and the quality of the batches cannot be assured. Deficient or non-conformance records also make investigations nearly impossible. This means that problems are more likely to occur without being detected – ie, changes in impurity profile, cross-contamination with other APIs due to ineffective cleaning, or altered crystal forms or particle sizes, which can impact bioavailability.

Drug Manufacturing

Approaches to Inspections in Asia

The European Medicines Agency (EMEA) and the US FDA are attempting to address these problems by inspecting API and pharmaceutical manufacturing sites in Asia.

The US FDA database lists almost 7,000 foreign firms that import pharmaceutical products into the US. There have been criticisms that the number of inspections performed on these firms by the US FDA have been unrepresentative of the number of products imported. According to Cherry Lau, Senior Technical Executive, SGS Hong Kong, only 13 out of 714 Chinese exporters of pharmaceutical products into the US were inspected in 2007. In comparison, 65 out of 410 exporters were inspected in India.

Records indicate that an estimated seven percent of all foreign API facilities are inspected by the US FDA each year, compared to 97 percent of US facilities inspected every two years. Many pharmaceutical companies in the US have expressed that this is unfair, especially given that the levels of controls, deterrents or sanctions on foreign facilities are not of the same standards.

In 2007, warning letters were issued by the US FDA to two Chinese pharmaceutical manufacturers for GMP non-compliance, resulting in a denial of entry of the latter's products into the US. This reflects a rather high proportion of non-compliance as the two companies were part of a group of 13 Chinese importers that were inspected.

The US FDA uses a risk-based process to develop a prioritized list of foreign establishments. Inspections are conducted on these companies to monitor the quality of their marketed drugs. Few inspections however, are completed in a given year.

According to the US FDA, about 30 such inspections were completed in 2007 and at least 50 were targeted for inspection in 2008. Figure 2 indicates the number of foreign inspections that were performed from 2002 to 2007.

There are currently many uninspected facilities that export their products to the US and Europe. This has also led to a situation where European API manufacturers are also selling their ingredients to the US, as they are unable to compete in Europe, with the lower cost (and often uninspected) Asian imports.

Inspections in exporting countries are expected to increase primarily in both China and India. The organization has already opened affiliate offices in Chinese cities such as Beijing, Shanghai and Guangzhou. It has also assigned about 13 employees to certify the inspections of US-bound Chinese exports.

	Number of inspections							
Country	FY2002	FY2003	FY2004	FY2005	FY2006	FY2007[a]	Total	Number of establishments[b]
India	11	19	38	33	34	65	200	410
Germany	24	15	35	25	19	22	140	199
Italy	17	30	26	21	18	19	131	150
Canada	29	12	17	23	23	19	123	288
United Kingdom	19	22	15	18	15	13	102	169
France	14	15	13	12	16	24	94	162
China	11	9	17	21	17	13	88	714
Japan	11	13	14	21	13	15	87	196
Switzerland	12	12	11	17	9	14	75	83
Ireland	11	5	11	14	3	11	55	61
All other countries	63	38	63	61	45	80	350	817
Total	**222**	**190**	**260**	**266**	**212**	**295**	**1,445**	**3,249**

Source: GAO analysis of FDA data.

[a]Inspection data for fiscal year 2007 may not be complete because FDA provided GAO with these data as of September 26, 2007, prior to the end of the fiscal year.

[b]This count represents the number of establishments FDA used to plan its fiscal year 2007 prioritized surveillance inspections.

Figure 2: The number of FDA inspections of foreign establishments involved in the manufacture of drugs for the US market – by country for the 10 most frequently inspected countries, fiscal years 2002 through 2007. (Source: GAO analysis of FDA data)

The foreign inspection process creates situations that are not encountered domestically in the US. For example, the US FDA relies on staff that inspect domestic establishments to volunteer for foreign inspections. Unlike domestic inspections, the inspection team does not arrive unannounced at a foreign establishment. There is also less flexibility to extend foreign inspections if problems are encountered, due to the need to adhere to an itinerary that typically involves multiple inspections in the same country.

Language barriers can make foreign inspections more difficult than domestic ones. The US FDA generally does not provide translators for its inspection teams. Instead, the teams may have to rely on an English-speaking representative from the foreign establishment being inspected, rather than on an independent translator.

Major Areas of GMP Concerns

According to statistical data based on inspection observations, the top 15 the major areas of GMP deficiencies by category are:

- **Quality system elements/procedures documentation**
- **Design and maintenance of premises**
- **Design and maintenance of equipment**
- **Process validation**
- **Procedures and facilities sampling**
- **Manufacturing documentation**
- **Potential for microbiological contamination**
- **Specification and testing documentation**
- **Facilities and equipment status labeling**
- **Environmental monitoring**
- **Supplier and contractor audit and technical agreements**
- **Equipment validation**
- **Hygiene/clothing**
- **Duties of key personnel**
- **Potential for chemical/physical contamination**

With the rising costs of pharmaceutical products and the emergence of low-cost competitors, manufacturing efficiency is becoming more important to Asian API manufacturers.

These deficiencies are an indication of a lack of understanding or commitment to GMPs. These types of GMP deficiencies cause concern among regulatory agencies, pertaining to the import of APIs and other drug related materials utilized in the production of finished drug products. There is a possibility that adulterated products may enter the US or European markets, due to either a lack of proper inspections or to the oversight of foreign companies.

There should be harmonization and guidance between the regulatory agencies and finished-drug manufacturers with supervision and inspections of foreign imports of APIs. To date, there has been a lack of guidance documents relating to the standardization of the auditing of APIs or other drug materials used in finished drug products. As a result, auditing standards are left up to the finished drug manufacturers who are sometimes under pressure to accept a vendor, based on cost and efficiency, rather than on quality and GMP compliance.

This is one of the reasons why there should be discussions on the development of global harmonization for second and third-party GMP auditing standards for the pharmaceutical industries.

Another suggested resolution is to have the regulatory agencies to certify or give approval to consultants or consultant companies to act on the agencies' behalf – to perform foreign inspections as per standard auditing practices.

Asian pharmaceutical and API suppliers require solutions that will enable them to ensure regulatory compliance and to address the global concerns on quality and authenticity. **PA**

Enquiry code: 094E05

Pharmacovigilance: Playing by the Rules

Variations in the regulations of different countries can present challenges for pharmaceutical companies.

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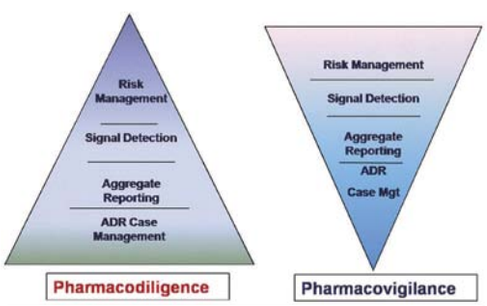


Figure 1: A comparison of approaches. (Source: GVK Biosciences)

The global pharmacovigilance scenario is changing both in terms of regulations and the efforts being undertaken by the regulators, pharmaceuticals industry, academia and healthcare professionals. Existing regulations are being revised and new regulations are being framed in several countries. However, gaps continue to exist as there is no harmonized regulatory approach and there are disparities in regulatory requirements that exist in many countries. Interestingly these gaps exist not only between the regulations of the developed and developing nations but also within the developed world.

The evolution of pharmacovigilance regulations in a particular country is dependent on several factors where the government plays a key decision-making role. The US, EU and Japan constitute the largest pharmaceutical markets and their regulations are some of the most stringent in the world. Elsewhere, the emerging markets are increasingly realizing the importance of pharmacovigilance and of constituting new regulations.

Differences in Approaches

Figure 1 illustrates the differences in the approaches taken by the pharmaceutical industry in the developing world compared to the industry in developed regions like the US, Canada and the EU. The approach taken by former can be termed as "Pharmacodiligence", represented by the triangle on the left, where the focus is on the collection of Adverse Drug Reaction (ADR) cases and reporting them within the expected timelines.

While companies invest in human and financial resources to comply with these regulations, there is minimal focus on performing risk-benefit evaluations on these cases. Such evaluations are perceived to be the responsibility of the innovator companies – almost all of which come from the developed world. The triangle on the right represents the approach taken by the industry in the developed regions, where the maximum effort is on risk management. This is the real purpose of pharmacovigilance, and pharmacodiligence is merely the means of achieving this endpoint, ie, determine risks and prevent ADRs.

From 1969-2002, about 2.3 million ADR cases were reported to the US FDA, of which about 80 percent originated from reporters in the US. It is likely that no country in the developing world would have received such a large number of ADR cases in the same time period. As America and the EU represent the bulk of the global pharmaceutical market, it is expected that most ADRs are reported from these regions.

Western society also has the mechanisms to conduct lawsuits on errant companies that compromise patient safety, and consumer alertness have also led to significant numbers of ADRs being reported. The governments of these countries also emphasize on public health and issue public safety alerts based on safety information that becomes available.

Government schemes like the Yellow Card scheme in the UK and MedWatch in the US ensure that consumers and Healthcare Professionals (HCPs) know where to report ADRs. In some countries it is even mandatory for the HCPs to report all ADRs that they are aware of. The media plays a significant role too, such that the first headlines of a significant safety alert may even appear in financial journals like The Wall Street Journal rather than in scientific health journals.

As the pharmaceutical market and its regulations continue to evolve in the developing countries along with increasing awareness among the consumers, the importance of pharmacovigilance is likely to grow. Perhaps this may give rise to a shift in approach from pharmacodiligence towards pharmacovigilance.

Protecting Public Health

The fundamental driving principle of pharmacovigilance is in safeguarding public health. The pharmaceuticals industry has an important role to play since it is at the center of the ADR information flow. In most cases, it is where the information is received (from patients or HCPs) and relayed to the regulatory authorities. The responsibility of industry goes beyond just collection and reporting. Also included in its list of activities are signal detection, risk-benefit evaluations and taking appropriate action to mitigate avoidable risks to the patients.

A robust pharmacovigilance system is essential for any pharmaceutical company. Regulatory authorities have instilled regulations and guidelines where non-compliance can lead to severe disciplinary action.

Many countries in the Asia Pacific region have well-defined pharmacovigilance regulations, eg, India, Vietnam, Malaysia, Australia, Japan and Singapore. Pharmaceutical companies with a headquarters in the region have expanded in the past few years and many have operations across the globe. Examples are India: Ranbaxy Labs, Dr. Reddy's Limited; China: Zhejiang Huahai Pharmaceutical, Zhejiang Hisun Pharmaceutical; Malaysia: Hovid.

Companies are under increasing pressure to adhere to local regulations. They also have to keep abreast and comply with the global regulations that are applicable in the countries where the companies' products have authorizations.

In order to sustain growth, companies need to increase their portfolio by either increasing the number of products in a certain market or the number of markets for a certain product. Both these scenarios demand either a setup of pharmacovigilance departments or an expansion of the existing capabilities.

Both innovator and generics companies operate in Asia. An observation is that the pharmacovigilance regulatory expectations in the region do not distinguish between generic and innovator companies. Therefore, generics companies need to sustain the same level of compliance to these regulatory obligations as much as their innovator counterparts.

There are however, issues that companies need to be aware of before implementing a pharmacovigilance system:

- **The Decision**

As the setting up and maintenance of a system can have huge cost implications, the question is whether a pharmaceutical company invest in such an initiative. The answer is affirmative as non-compliance may put patients at risk. A non-compliant company may also face problems such as penalties by regulatory agencies, product recalls and consumer lawsuits – leading to a decline in company share prices and the erosion of shareholder wealth.

- **Complex Systems and Processes**

Setting up a pharmacovigilance system for a relatively new company could be challenging due to a lack of expertise and resources. It requires knowledge, investments and inputs from various stakeholders within the company like regulatory affairs, information technology (IT), sales, finance, marketing, legal, manufacturing, quality assurance, human resources and third-party vendors.

Drug Manufacturing

Table 1: Examples of variations in global pharmacovigilance regulations. (Source: GVK Biosciences)

S. NO.	ACTIVITY	VARIATIONS	EXAMPLES
	Start of Pharmacovigilance responsibilities for a product		
1.	Pharmacovigilance obligations start date	From date of authorization	US, Canada, EU
		From date of launch of product in the market	India, Australia (expedited reporting)
	Variations in Expedited reporting standards		
2.	Timelines for submission	15 calendar days	US, EU
		10 working days for domestic cases	Vietnam
		5 calendar days	Business Partners Exchange
3.	Requirement for foreign/ domestic reports	Both foreign and domestic	US, EU, Japan, Ukraine (Only serious unexpected, fatal/ life threatening cases from confirmed company products
		Foreign reports not required	Mexico, South Africa, Malaysia, Brazil, Australia, Singapore, Thailand, China, Russia
4.	Medically confirmed versus unconfirmed cases	Accepted	US
		Not accepted	EU
5.	Published Literature monitoring for ADR cases	Required	US, EU, Australia (domestic only), Canada, Japan
		Not required	India, Latin America, Africa, Russia, CIS
6.	Different ADR reporting forms	MedWatch/ Council for International Organizations of Medical Sciences or CIOMS (for foreign cases only)	US
		CIOMS	Japan
7.	Electronic (E2B) reporting requirement	Mandatory	EU Competent Authorities and European Medicines Agency (EMEA)
		Not mandatory	Rest of world
	Differences in Periodic reporting standards		
8.	PSUR submission requirements	Mandatory requirement	US, EU, India
		On request by regulatory agencies	Canada, South Africa
		At license renewal only	United Arab Emirates
9.	PSUR submission cycles	Quarterly, annually	US
		Quarterly, semi-annually, annually, re-registration	Mexico
		Three years (harmonized birth date based)	EU
		Annually	Australia
		Registration, re-registration	Kazakhstan, Ukraine, Russia, Belarus, Iran, UAE, China
10.	Content of PSUR	The following sections of a PSUR are not required: patient exposure, literature search, detailed marketing authorization status	US
		Comprehensive data is required per volume 9A, including all sections listed above	EU
		Literature search not required	India
		Additional requirement of write up about company's pharmacovigilance systems	Kazakhstan
		Additional requirement of executive summary in Portuguese. PSUR content can be in English	Brazil
11.	Timelines for submission of PSUR from the Data Lock Point (DLP)	30 – 60 days (quarterly/annual)	US
		60 days	EU, Brazil
		30 days	India
	Variations in Risk Management Plan/Program requirements		
12.	Risk management program eg, Isotretinoin risk management	iPledge program mandatory	US, Canada, EU
		Not mandated by any other agency	Rest of the world
13.	Risk management plan submission mandatory	For all new registrations	EU
		Not mandatory for all registrations	Rest of the world

The systems need to work in harmony to deliver the following outputs in an efficient manner:

1) Customer call receipt and triage
2) ADR case processing & reporting (electronic or hard copy)
3) Periodic safety update reporting (PSUR)
4) Product quality complaints management (included by some companies)
5) Medical inquiries management (included by some companies)
6) Electronic safety database validation
7) Safety data exchange agreement management
8) Signal detection – risk-benefit evaluation
9) Risk management programs
10) Literature monitoring for ADR case reports
11) Training of company employees on ADR reporting
12) Global compliance monitoring
13) Audits and inspections management

- **Lack of Harmonization in Global Regulations**

Although global pharmacovigilance regulations have evolved from the same initial idea, there are some differences in different regions – posing another challenge for companies with global operations.

An up-to-date knowledge of international regulations is essential. In many regions, the regulations are being revised and updated (eg, European Economic Area or EEA) and it is essential to keep pace with these changes. Examples of some variations can be found in Table 1.

- **Large Product Portfolio**

How does one construct a foolproof system for the pharmacovigilance of several thousand global authorizations? Some generics companies have operations in more than 100 countries where there may be different authorizations (various strengths and formulations) in each of these countries for the same active ingredient. Handling such a large portfolio of products may turn

out to be a management nightmare. In addition, mergers and acquisitions can also add to the complexity.

In order to penetrate new markets, overseas organizations are increasingly entering into business agreements with local companies in Asia. The pharmacovigilance obligations however, still remain and these companies need to define their responsibilities in the form of Safety Data Exchange Agreements (SDEA). These SDEAs form a legal binding tool that defines the role of each company.

- **Knowledge & Manpower**

Pharmacovigilance is a knowledge-intensive area of expertise. Since it is still a relatively new field in many Asia Pacific countries, there is a limited availability of people who are trained in this area. Table 2 illustrates the basic skills required for a pharmacovigilance employee.

Table 2: Basic skills required for a pharmacovigilance employee. (Source: GVK Biosciences)

Activity	Basic training
Call receipt and triage, case entry into database	Life sciences graduates/medical background
ADR case processing, PSUR, signal detection, safety data exchange agreement management, risk management plans	Medical graduates/post graduates
Safety database validation	IT graduates/post graduates with the knowledge of pharmaceutical industry computer systems validation requirements

- **Different Countries, Linguistic barriers**

There are also challenges in terms of differences in language (see Table 3).

Table 3: Examples of challenges due to linguistic barriers. (Source: GVK Biosciences)

Activity	Example
Call Centre for customer calls for receipt of ADRS	Centralized call center requires multi-lingual skills eg, a call centre in the EU requires personnel with knowledge of several languages
Communication with regulatory agencies' requirement of local language covers letters, PSUR executive summary	Brazil, Russia
Local submission of ADR case reports	Native language is preferred in China , Japan, Brazil
Country operations management	Eg, Brazil (Manager should know Portuguese, Spanish, English. The language most commonly spoken in Brazil is Portuguese, while Spanish is for the rest of Latin America.

- **Evolving Regulations**

As regulations evolve, they tend to become more specific and stringent. Companies need to enhance their knowledge, manpower and processes to cope with these updates. This could mean making drastic changes to already existing process workflows. Table 4 provides examples of changes in global regulations.

Table 4: Revisions in global pharmacovigilance regulations. (Source: GVK Biosciences)

Regulatory Agency	Year of Last Update
Brazil	February 2009
Vietnam	March 2009
EU	Vol 9A – September 2008
Russia	November 2008
US	Though CFR are final, however the guideline for post marketing pharmacovigilance was released in 2001 as a draft guideline.
Mexico	2007
Ukraine	2007

- **Emotional Sensitivity**

A consumer's perspective could add another dimension to pharmacovigilance – emotional sensitivity. This sensitivity could be further influenced, in a detrimental way, by media overreaction over reports of ADR which are known to occur with a particular drug. Physicians may also be skeptical about reporting ADRs to the company, thinking that this may affect their own image and reputation.

There may be sensitivities due to cultural variations. In a conservative society for example, inquiring about the pregnancy status of a young teenage girl as a part of a risk management program like iPledge for isotretinoin, could be deemed inappropriate by the patient. Therefore, certain local adaptations in procedures at a local level may be needed.

- **Product Liability Implications**

A general public perception in certain regions may be that if a company is reporting ADRs on a regular basis compared to another company that is not reporting as many ADRs,

Table 5: Key differences between the "in-house" and "outsourcing" models. (Source: GVK Biosciences)

	In-House	Outsourced to CRO
1.	In a pharmaceutical company with manufacturing capabilities, the focus is high on core competence areas eg, manufacturing, sales and marketing. Compliance-related activities which are perceived as cost overheads for the company and do not yield revenue directly are likely to receive less attention	Pharmacovigilance activities areas are core activities for CROs that specialize in this domain and have a knowledge base. These activities receive prime importance and compliance is considered sacrosanct.
2.	Overheads for maintaining compliance to pharmacovigilance obligations are high. For example, maintaining a safety database is expensive	Overheads get distributed over several clients.
3.	Scalability is not easily achievable when new companies are acquired or when expansion into new markets takes place, as there is a cost implication	Economies of scale bring costs down
4.	Experience is limited and there is a likelihood of losing highly skilled personnel	Experience is wider, gained from servicing several clients with a widespread reach and greater knowledge base
5.	Capital cost of software applications setup and maintenance	Various models suitable to the client's needs can be worked out to make it more affordable for the client
6.	Viewed by internal management as a cost center and not as a profit center	Viewed as a profit center by the CRO, hence provides higher quality services
7.	The need to achieve compliance may be a distraction from main business of selling drugs	Main business focus is service, so compliance is sacrosanct.

the quality of former's product is probably not as good as that of the latter. Certain regulatory authorities may also share this perception, leading to heightened anxiety for the company that is rigorously following pharmacovigilance best practices.

- **Cost Implications**

A good pharmacovigilance system is dependent upon Information Technology (IT) systems and human resources. There are various commercially available safety database systems which provide a backbone to the data management of ADR cases. These software applications serve as repository of ADR cases from across the globe and can be configured to schedule reports for global regulatory authorities and the analysis of the data for signal detection.

However, these systems are expensive to purchase and maintain and require validation efforts before they can be put to use. The majority of the cost component can be attributed to the following activities: cost of the software, licenses, hardware, validation of the database, implementation of the company's specific workflow, annual maintenance, training, recurrence cost of IT platform license, Medical Dictionary for Regulatory Activities (MedDRA) Dictionary subscription, World Health Organization Drug Dictionary (WHODD) subscription, third party application licenses, software upgrades/new versions, extra features/customizations.

Even with the use of varied software, pharmacovigilance continues to remain a labor-intensive activity. Personnel are required for data entry, quality control, medical review, generation of periodic reports, signal detection activities and the maintenance of these systems.

Business Models – In-House vs Outsourcing

Given the complexities in managing these challenges, companies choose from various types of operating models, namely the "outsourcing model" or the "in-house model". Both these models have their respective strengths and weaknesses and the choice of model is dependent on certain key determinants.

Any company, either generic or innovator can follow any of the following business models for pharmacovigilance:

1. **All activities in-house**
2. **Partial activities outsourced to a Contract Research Organization (CRO)**
3. **All activities outsourced to CRO**

Activities that can be outsourced to a CRO include:

- Expedited reporting: Capture of ADRs in an electronic database, quality control, medical review and analysis of Individual Case Safety Reports (ICSR), Reporting (E2B, CIOMS)
- Periodic reporting: Generation of PSURs, narrative writing, etc.

- Monitoring of ADR literature
- Safety data exchange agreements
- Validation of electronic safety database
- Signal detection activities
- Product quality complaint management
- Medical inquiry management
- Risk management programs
- Training of company employees on ADR reporting
- Pharmacovigilance audits
- Department setup/restructuring

Each model has its own pros and cons. Keeping all activities "in-house" offers greater control on the flow of data; however it can be expensive and time consuming to setup and update. Table 5 provides some of the differences between the "in-house" and "outsourcing" models

Pharmacovigilance related expenditure is a "bitter pill" that every responsible pharmaceutical company has to swallow. However, this pill is necessary for ensuring patient and public safety. A robust system at the industry and state level can ensure that unnecessary and avoidable risks to the patient are minimized. The challenges for achieving this are many and the right approach can help to ensure that the desired results are achievable. **PA**

Enquiry code: 094E06

Talent Acquisition in Emerging Markets: More than Just the Money *(Part Two)*

In the second part of our series, studies show that it takes more than just attractive remuneration to hire and retain executives.

Martin Reynolds,
CEO,
Sharpstream Life Sciences

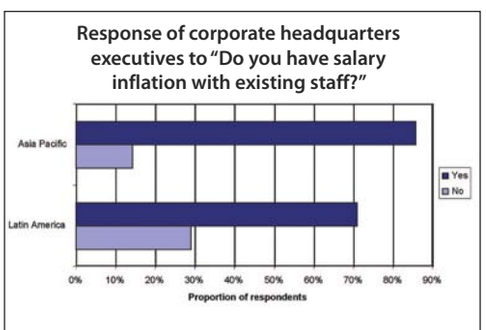


Figure 3.5: Salary inflation is a particular problem in both Asia-Pacific and Latin America. (Source: Sharpstream Life Sciences)

If talent is scarce, its price will be driven up. Fully 86 percent of executives surveyed at corporate headquarters agree that salary inflation is an issue with existing staff in the Asia-Pacific region.

Even in Latin America, where the talent shortage is not seen as being such an important issue, 71 percent of interviewees at corporate headquarters identify salary inflation as being a problem. This is supported by Hewitt Associates, which reports that workers in Latin America experienced the second-highest salary increases in the world in 2007 (just behind Asia Pacific). Hewitt reported average 2007 salary increases of 16 percent in Venezuela, 13 percent in Argentina, 5.9 percent in Brazil, and 4.9 percent in Mexico.

Meanwhile in Asia Pacific, evidence for continuing salary inflation is supported by Mercer's 2008 Global Compensation Planning Report, which predicts average across-the-board annual salary increases of 14.1 percent for India, 11.9 percent for Vietnam, 7.5 percent for China and 6.4 percent for South Korea. These figures compare with average increases of just 3.7 percent for the US and around 3.0 percent for Western Europe.

The evidence for salary inflation is supported by another section of the study, in which the in-market interviewees were asked to discuss their salary expectations if they were seeking a move to another company. Most expect an increase in basic salary of around 20 percent for a lateral move to a position at the same level, with the average expected increase being 21 percent in Asia-Pacific and 18 percent in Latin America. This is almost as much as the expectation for a move to a position at a higher level, for which the average expected increase would be 27 percent in Asia-Pacific and 29 percent in Latin America.

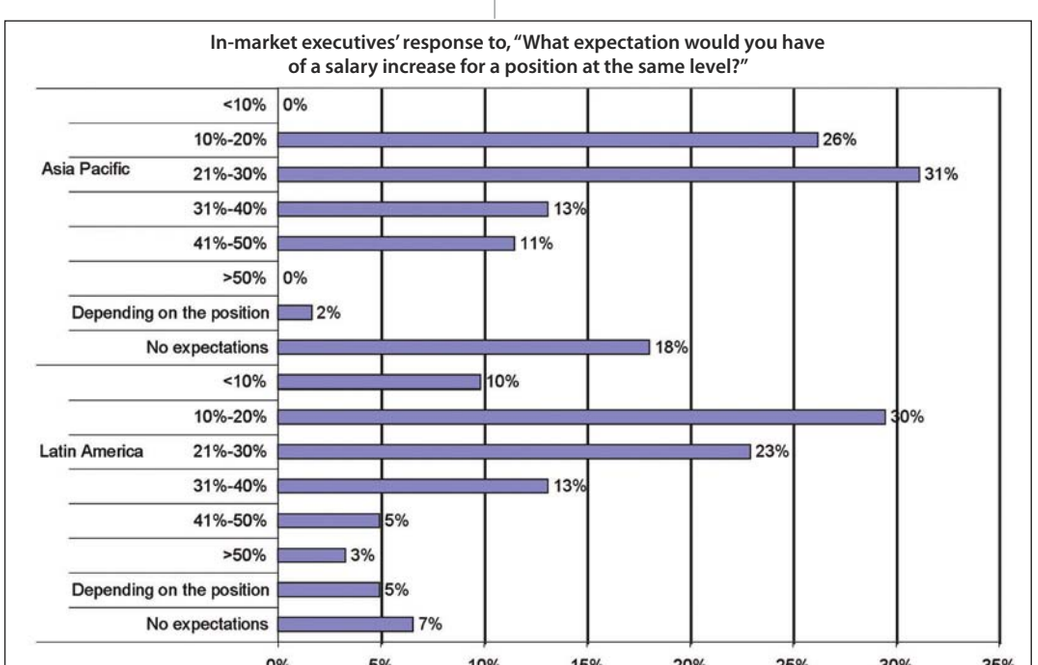


Figure 3.6: Salary inflation is reflected in the in-market executives' salary expectations. (Source: Sharpstream Life Sciences)

Career Motivations and Expectations

In order to attract top talent in emerging markets, it is important to understand their career motivations and expectations. These executives know they have a choice. They may want to choose organizations with a strong brand or good ethical reputation; they may be attracted to working with high profile industry leaders; or they may simply be motivated by material rewards.

To explore these elements in some detail, the in-market executives were asked to rank various factors associated with potential future positions in order of importance. The executives at corporate headquarters were also asked to rank what they considered to be important factors influencing an individual's choice

when deciding on a future employer. The results are illustrated in Figure 3.8, Figure 3.9, Figure 3.10, and Figure 3.11.

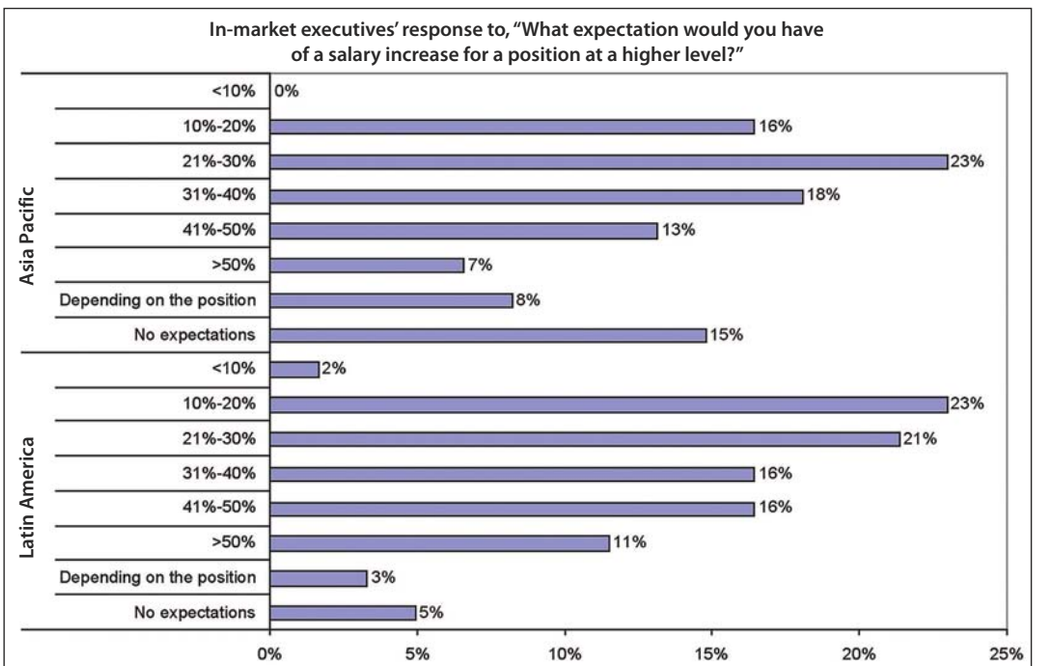


Figure 3.7: Salary inflation is reflected in the in-market executives' salary expectations. (Source: Sharpstream Life Sciences)

- **Profile of the Position**

Most of the interviewees see the Profile of the Position as being the most important factor in a future job, with this ranking first in Asia-Pacific and second in Latin America. Clearly, and unsurprisingly, these high-potential executives are ambitious, motivated individuals, and they expect to see themselves in high profile positions in the future. However, this ambition is not recognized at corporate level; in the responses of the corporate headquarters interviewees, just seven percent in Asia Pacific and 16 percent in Latin America rate the Profile of the Position this highly.

- **Learning and Development**

The in-market executives interviewed also like to challenge themselves and learn, and see the potential for this as being integral to any future career move; well over 95 percent of interviewees in both regions see a Learning or Development Opportunity as being at Least Important, with 50 percent of those in Asia-Pacific and 67 percent in Latin America seeing it as Most Important.

Worryingly, not many corporate headquarters respondents with responsibility for Asia-Pacific see it the same way; a mere 14 percent rate Learning or Development Opportunity as being a major factor influencing potential recruits. More encouraging was the finding that some 42 percent of headquarters executives with Latin America responsibilities recognized the importance of this component.

- **Company Reputation**

Although corporate leaders in both regions see the Reputation of the Company as being the most important factor for attracting and retaining talent, the talent itself does not agree. In Asia-Pacific, only 43 percent of interviewees feel this way, so that it is ranks only fourth in terms of overall importance. It is held in higher regard in Latin America, however, and features in the top three reasons to join a company, with 67 percent of respondents giving it a Most Important ranking.

- **Profile of Management**

The most striking difference between the two regions is the ranking of Profile of Direct Manager. In Asia-Pacific this factor ranks second in overall importance, with 69 percent of interviewees ranking it as Most Important, just a few percentage points less than the Profile of the Position.

This compares with just 23 percent in Latin America, where it ranks below other factors such as Regional Strategy of the Company or the Profile of the Company's Products. This finding perhaps indicates the value attached to personal relationships that are an aspect of business life in China in particular; Chinese workers are characteristically committed to the individual rather than the company. It could also be that that executives in Asia-Pacific are more attracted by the prospect of working with someone who is recognized as an industry

leader and can instill the knowledge and skills that are required for in moving their career forward.

In any event, this is another element whose importance appears to be underestimated by corporate headquarters with regard to recruitment strategy; in the survey of corporate leaders, the Profile of Management is ranked last in terms of importance in Latin America and third last in Asia-Pacific. **PA**

Table 3.1: Top three factors motivating in-market executives to make a career move. (Source: Sharpstream Life Sciences)

Rank	Asia-Pacific	Latin America
1	Profile of the Position	Learning & Development Opportunity
2	Profile of Direct Manager	Profile of the Position
3	Learning & Development Opportunity	Reputation of the Company

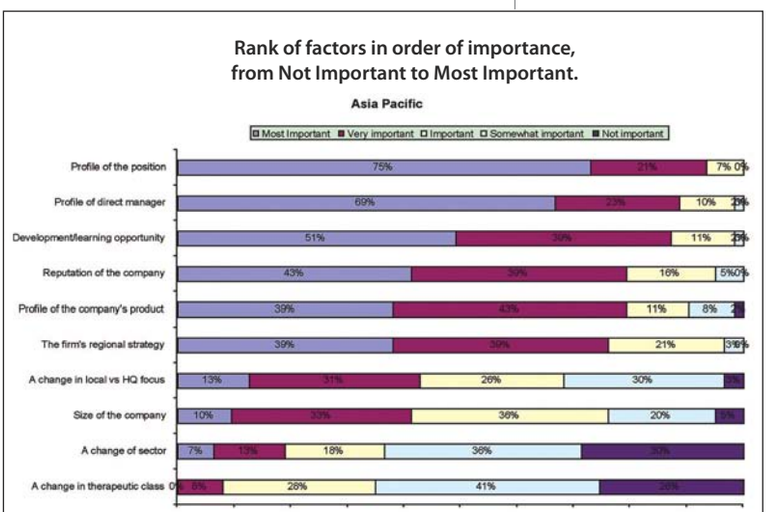
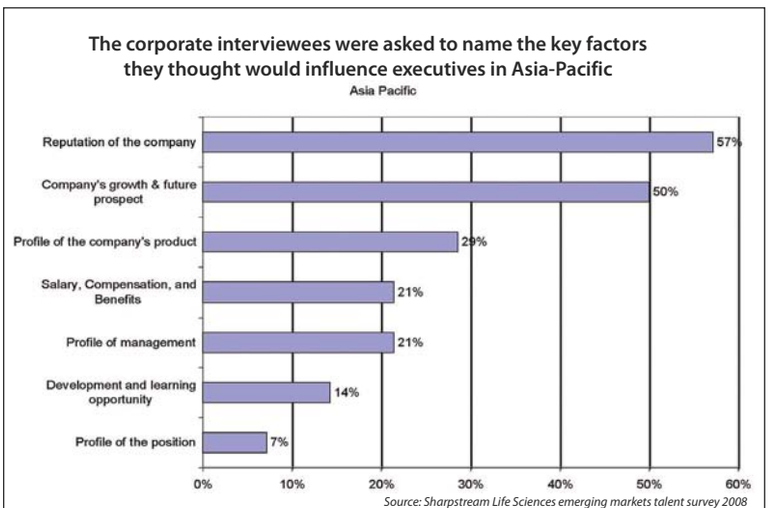


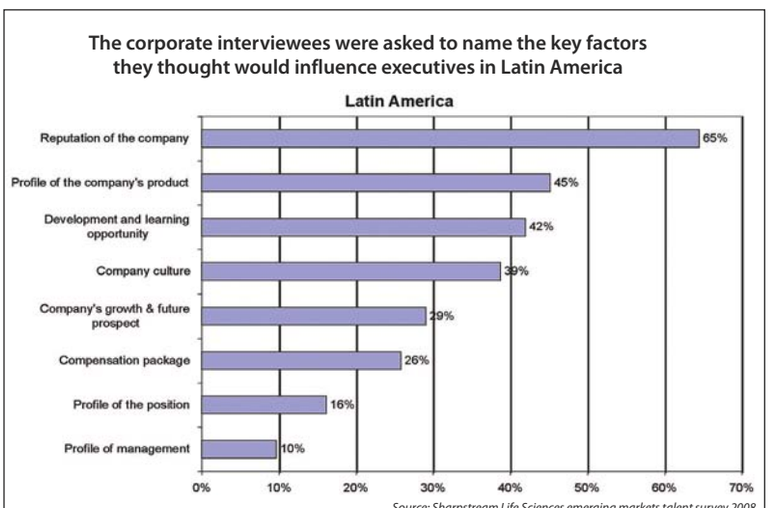
Figure 3.8: Leading factors motivating in-market executives in Asia-Pacific to make a career move. (Source: Sharpstream Life Sciences)



Source: Sharpstream Life Sciences emerging markets talent survey 2008

Figure 3.9: Corporate HQ perceptions of leading factors motivating in-market executives to make a career move in Asia-Pacific. (Source: Sharpstream Life Sciences)

Figure 3.10: Leading factors motivating in-market executives to make a career move in Latin America. (Source: Sharpstream Life Sciences)



Source: Sharpstream Life Sciences emerging markets talent survey 2008

Figure 3.11: Corporate HQ perceptions of leading factors motivating in-market executives to make a career move in Latin America. (Source: Sharpstream Life Sciences)

Part three of the series will be featured in the Aug issue of PharmaAsia

Enquiry code: 094E07

API/Interphex China

Previously a show that catered largely to the domestic market, API/Interphex China is gaining attention in the international pharma space. ***Michael Tham*** reports

The Show is held twice a year, in spring and autumn. Daniel Chan, director, Reed Sinopharm Exhibitions explains, "The spring event sets the pace for the industry for the new year in terms of distribution channels, pricing and strategy. The unique feature of the show is its exhibitor profile – Chinese manufacturers (rather than traders) of Active Pharmaceutical Ingredients (API). We see it as the 'brotherhood bonding event' of the industry."

Conferences are centered on the mega-trends and the strategic direction of the industry, and explore ways to enhance the future growth of API in China.

Since its launch, the show has been predominantly China-centric and focused on domestic trading. With globalization, the needs of the industry are evolving and the show is taking on a global perspective.

The Sino-India Partnership Program (SIPP) aims to create a platform for Indian and Chinese companies to do business. "We are hoping that this platform can also facilitate cooperation between the governments of both countries in further developing the industry. The India Buyer Port (IBP) provides booths for Indian buyers – to aid them in their sourcing for API manufacturers in China," says Chan.

D G Shah, Secretary General, Indian Pharmaceutical Alliance emphasizes the need for greater cooperation between the governments of India and China.

D G Shah, Secretary General of the Indian Pharmaceutical Alliance emphasized the need to encourage two-way trade in pharmaceutical and bio-tech products between India and China. He pointed out that it is necessary for both countries to leverage on each other's strengths and demolish barriers to entry. Shah also recommends that the countries work together to overcome the challenges faced by the generics industry.

Held in the ancient Chinese city of Xi'an from May 12-14, this edition featured more than 1,200 exhibitors over an area of 55,000 sqm. It was attended by 30,000 local and international visitors. **PA**

Show Report

Sino-India Co-operation

Chirag Doshi,
Hon Secretary,
The Indian Drug Manufacturers' Association

The Indian Drug Manufacturers' Association (IDMA) – Gujarat State Board plays a supporting role by helping its members to understand the Chinese market, and to procure pharmaceutical ingredients and materials. The association organized road shows in India about two months ago to encourage Indian visitors to attend API China. This show is quite different from other shows as its exhibitors are the actual manufacturers of Active Pharmaceutical Ingredients (API).

Some of the other pharmaceuticals shows tend to have a higher percentage of exhibitors who are traders rather than manufacturers. In sourcing for raw materials, the problem that some buyers face, is that traders may not be interested in doing business where the volume is below the latter's expectations. This is because traders normally operate on a commissions-based structure. Manufacturers on the other hand tend to be more receptive towards buyers of smaller volumes of ingredients.

About 60 percent of the global API supply comes from China. In addition, there are also certain ingredients which can only be found in the country. India's pharmaceuticals industry has a stronger emphasis on formulations manufacturing and has to depend on China for APIs. **PA**

Product Innovation

Joe Nip,
Chairman,
Jiangsu Zodiac Marine Biotechnology

Widjaja Suryani,
MD

Our company uses a type of seaweed extract called carrageenan for the capsules that we manufacture for the pharmaceuticals industry. Generally speaking, carrageenan is usually used in food products. Our company is the only one in China that uses this type of seaweed extract for making capsules. Seaweed-based capsules have several advantages over the gelatin equivalent. One of these is the absence of protein, creating conditions that do not support bacterial growth.

We currently have three manufacturing plants. Two of these plants manufacture the raw materials that are required for capsules. The first is located in the Guandong province. In 2007, we invested US$20 million to build a second plant in the province of Jiangsu. The third plant manufactures capsules.

We have an annual production output of two billion capsules with a revenue of US$10 million.

The seaweed capsules are still a relatively new product from our company and we are just starting to market it. Presently, we expect most of the demand to come from countries like the US, the Middle East and Europe. As this product costs twice as much as gelatin capsules, we expect less local demand at this point in time as this market is more price sensitive.

In the next three to five years, we expect to achieve a sales turnover of US$50 million. **PA**

Shanben Zhu,
General Manager,
Changzhou Runde Medical Materials Factory

Customized Production

Our company produces packaging materials such as rubber bungs and Polypropylene (PP) caps for vials and containers. These products are suitable for use with liquids and powdered materials. Our customers are drug manufacturers who work with various chemicals and ingredients to develop new drugs. Our R&D center conducts research to determine the types of materials that are needed for the manufacture of bungs that meet the specific requirements of each client.

Our production facilities are also designed and constructed in accordance to Good Manufacturing Practice (GMP).

The domestic market accounts for about 80 percent of the company's sales. The rest are exports to destinations such as Japan, Europe, Turkey, Egypt and the US. In the next two to three years, we expect to see a shift with 30-40 percent being export sales. We plan to achieve this by expanding into the Russian market. We also have plans for further market expansion into India.

The annual revenue of the company in 2009 is expected to be two billion Yuan (US$0.3 billion). Sales revenue has been increasing by 20 percent every year.

The company is a member of the Chinese Pharmaceutical Packaging Association. **PA**

Overseas Expansion

Li Yan,
GM,
Qilu Pharmaceutical Co

Our company focuses on the development, manufacture and marketing of generic drugs. We specialize in therapeutic areas such as oncology, cerebrovascular and cardiovascular, infections, psychology and neurological system, respiratory system, ophthalmological diseases. We also manufacture APIs.

Our manufacturing sites have been approved by foreign regulatory agencies such as the US Food and Drug Administration (FDA), European Directorate for the Quality of Medicines (EDQM), and Medicines Control Council (MCC) of South Africa.

About 30-40 percent of our exports (APIs) go to companies in India, with the majority being made up of anti-infectives. Our customers there include companies such as Cipla, Strides and AstraZeneca.

Our employee headcount was 4,500 as of 2008. Revenue increased from US$260 million in 2005 to US$570 million in 2008. We expect this figure to reach US$740 million in 2009. Similarly, we expect our exports to grow from US$70 million in 2008 to US$90 million in 2009.

Our largest export market is Europe. This is followed by India and then South America. **PA**

Frank Sun,
Manager,
HYS Ocean Biotechnology Industrial Co

Mass Production

HYS Ocean Biotechnology produces soft gel capsules, tablets and hard capsules. We have been producing the soft gel capsules since 1996 and currently have 14 Korean-made machines that gives us a production capacity of five billion capsules per year.

The company exports about 10 containers of soft gel capsules to the US, Canada and Europe. We produced about three billion capsules last year and are expecting to produce four billion capsules this year.

We are also exporting to countries such as South Africa, Columbia, Hong Kong, the Philippines and Indonesia. Exports account for about half of our production. **PA**

Show Report

Feng Sheng Xi,
Deputy Director
Guangzhou BaiYunShan (BYS)
Chemical Pharmaceutical Factory

Maintaining Quality

BYS has eight factories for the production of formulations and one for API. All are located in China. We also cooperate with other organizations such as hospitals to conduct clinical trials.

About 80 percent of our product is sold domestically while 20 percent is exported. India alone accounts for about eight percent of total sales. Other destinations include South America, Korea, Pakistan and the Middle East.

Our products include ceftazidime, cephradine, ceftriaxone and cefotaxime. There are certain products that we can produce more cheaply than our India-based competitors, for example, cephradine. This is because the raw materials for such products are available domestically at a lower cost compared to other countries like India.

We have a Quality Assurance and Quality Control department that develops and maintains our manufacturing systems according to cGMP.

China's SFDA is improving on its GMP standards. I believe that it will be similar to cGMP standards from the European Directorate for the Quality of Medicines and HealthCare (EDQM). **PA**

Prince Qian,
Sales & Marketing Manager
Xi'an Ruilian

Achieving Standards

Our company was established in 2001, specializing in Liquid Crystal (LC) materials and technology. In 2006, we started producing pharmaceutical intermediates.

The company achieved US$60 million in sales last year and we are projecting this figure to grow to US$75 million in 2009. Exports account for about 95 percent of our products.

LC and pharmaceuticals are both organic chemicals and have similar production requirements. For example, both require the same ultra-clean conditions for their manufacture. This allowed us to leverage on our expertise in LC production when we made the move to pharmaceutical intermediates and API manufacturing.

We have achieved the ISO9001:2000 and ISO14001:2004 certification and are aiming to attain the US Food and Drug Administration (FDA) certification by 2012.

Our manufacturing facilities are subject to audits by inspection teams representing our customers such as Novartis, AstraZeneca and Sandoz – to ensure GMP compliance. **PA**

Liu Zhilin,
Exports,
Hebei Shengxue Glucose

Market Growth

We produce 30,000 tons of dextrose anhydrous, 10,000 tons of dextrose anhydrous, and 3,000 tons of xylitol and 5,000 tons of Xylose per year. Next year, we will be increasing our existing production capacity of xylitol by 5,000 metric tons per year. Our customers include Baxter in the US and Otsuka in Japan.

We export our products to Japan, Indonesia, Thailand, Korea, Europe and India. The local Chinese market is still our most important market that takes up 20,000 tons of our production.

Our revenue from the Indian market is about US$500,000, out of a total export revenue of about US$20 million. Our total sales revenue is US$45 million.

The company has attained certification in the State Food and Drug Administration (SFDA) Good Manufacturing Practice (GMP), International Organization for Standardization (ISO) 9001, and Hazard Analysis and Critical Control Points (HACCP).

Hebei Shengxue Glucose is located in the Luancheng industrial zone. Our factory spans an area of 100,000 sq meters. It is 270 km from Beijing and 400 km from the Tianjin Seaport. **PA**

Enquiry code: 094E08

Product Focus
Pipetters/Filtration

Automated Pipetting Station Reduces Protocol Cycle Time

The Vertical Pipetting Station from Agilent Automation Solutions features a choice of easily interchangeable 8-, 16-, 96-, and 384-channel heads. A two-axis positioning stage provides access to all quadrants of 96-, 384- and 1536-well microplates.

The station features eight pneumatic sliding shelves arranged on either side of the pipetting head permitting access to plates, while conserving deck space. The shelves can be custom fitted with vacuum manifolds (to position warped PCR microplates), autofilling reagent shelves, or a tip-washing station. **Agilent**

Enquiry code: 094P01

Biohit: Consistent Loading and Ejection

The Optiload from Biohit is a tip loading mechanism for the easy, safe and consistent loading and ejection of tips from single and multichannel pipettes.

With the "Systems" approach, the fit between the tip and pipette tip cone is optimized, allowing accuracy and precision in the delivery of liquid samples.

The tips seal securely and will not fall off. They also do not require excessive force to load onto or eject from tip cones. **Biohit**

Enquiry code: 094P02

Electronic Pipetters Increase Liquid Sample Transfer Productivity

Available from Integra Biosciences, the Viaflo Voyager range of handheld 8- and 12-channel electronic pipetters are designed to increase the productivity of liquid sample transfers.

Based on a motorized adjustable spacing design, the pipetters eliminate cross contamination and ensure the consistent, accurate delivery of liquids to target vessels. The electronic pipetters are suitable as a liquid handling tool for applications including sample reformatting, Polymerase Chain Reaction (PCR) set-up, Enzyme-Linked Immunosorbent Assay (ELISA) sample transfers and Taqman Assay set-up.

The 8-channel pipetters serve as an efficient tool for transferring fluids out of tubes in racks that are spaced more than 9.0mm apart into 96-well format plates. Eight transfers can be done simultaneously with only one hand. **Integra**

Enquiry code: 094P03

Efficiency in Filtration Operations

Millipore Corporation has launched its range of four Mobius FlexReady Solutions. The range is made up of single-use filters and assemblies and process-ready hardware platforms optimized for clarification, media and buffer preparation, tangential flow filtration (TFF) and virus filtration unit operations.

Users can install equipment, configure applications and validate their processes quickly and easily. The pre-assembled, pre-tested Flexware assemblies include technologies such as Millistak+ Pod filters; Pellicon 3 TFF cassettes, Viresolve Pro parvovirus removal filters, Express sterilizing-grade filters and Lynx connectors; as well as Mobius MIX disposable mixing systems and storage systems. **Millipore**

Enquiry code: 094P04

Membrane for Precise Filtration

The Anopore inorganic membrane (Anodisc) from Whatman is suited for a range of laboratory filtration applications. This material has a precise, nondeformable honeycomb pore structure with no lateral crossovers between individual pores. It filters at the stated cut-off and does not allow larger sized particles to pass through the membrane.

The membrane is composed of a high purity alumina matrix that is manufactured electrochemically. The membrane also exhibits low protein binding, has minimal autofluorescence, is nontoxic, and supports cellular growth.

The pore structure and narrow pore size distribution of the membrane ensure particle removal efficiency. Microorganisms and particulate material are captured on the surface of the membrane for subsequent analysis by light or electron microscopy. When wet, the membrane is virtually transparent, which means that retained particles do not need to be transferred to another surface before microscopic examination. **Whatman**

Enquiry code: 094P05

Calendar of Events

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

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

July 1 – 3, 2009
Global Pharmaceutical Fraud &
Anti Counterfeiting Conference
Singapore
www.globalpharmafraud.com

Jul 9 – 10, 2009
China Medical Trials and Safety Surveillance
Shanghai, China
www.noppen.com.cn/Old_Corporate_
Website/HTML/medical_devices/home.html

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

Aug 24 – 25, 2009
Pharmaceutical Regulatory Affairs 2009
Sheraton Towers, Singapore
www.ibc-asia.com/regulatory

Aug 26 – 27, 2009
OTC Pharma Asia: Capitalizing on
New Market Development & Building
a Sustainable Growth Strategy
Singapore
www.abf-asia.com

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

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

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

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

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

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

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

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

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

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

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

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

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

AD INDEX

Biopharmaceutical Production Series

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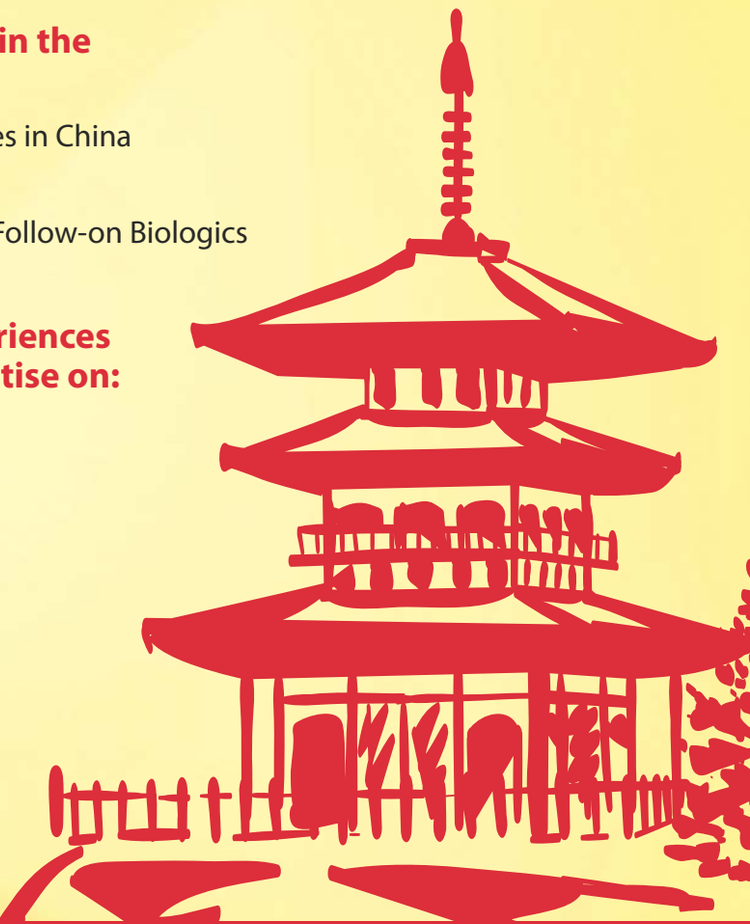

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