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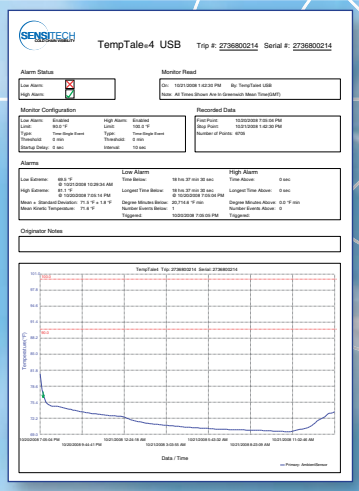

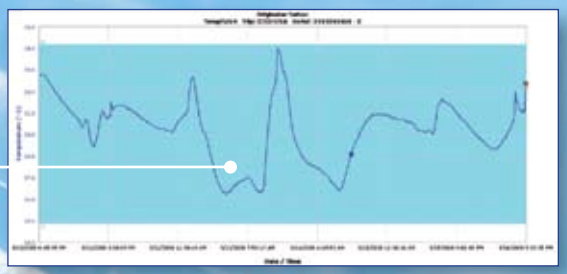

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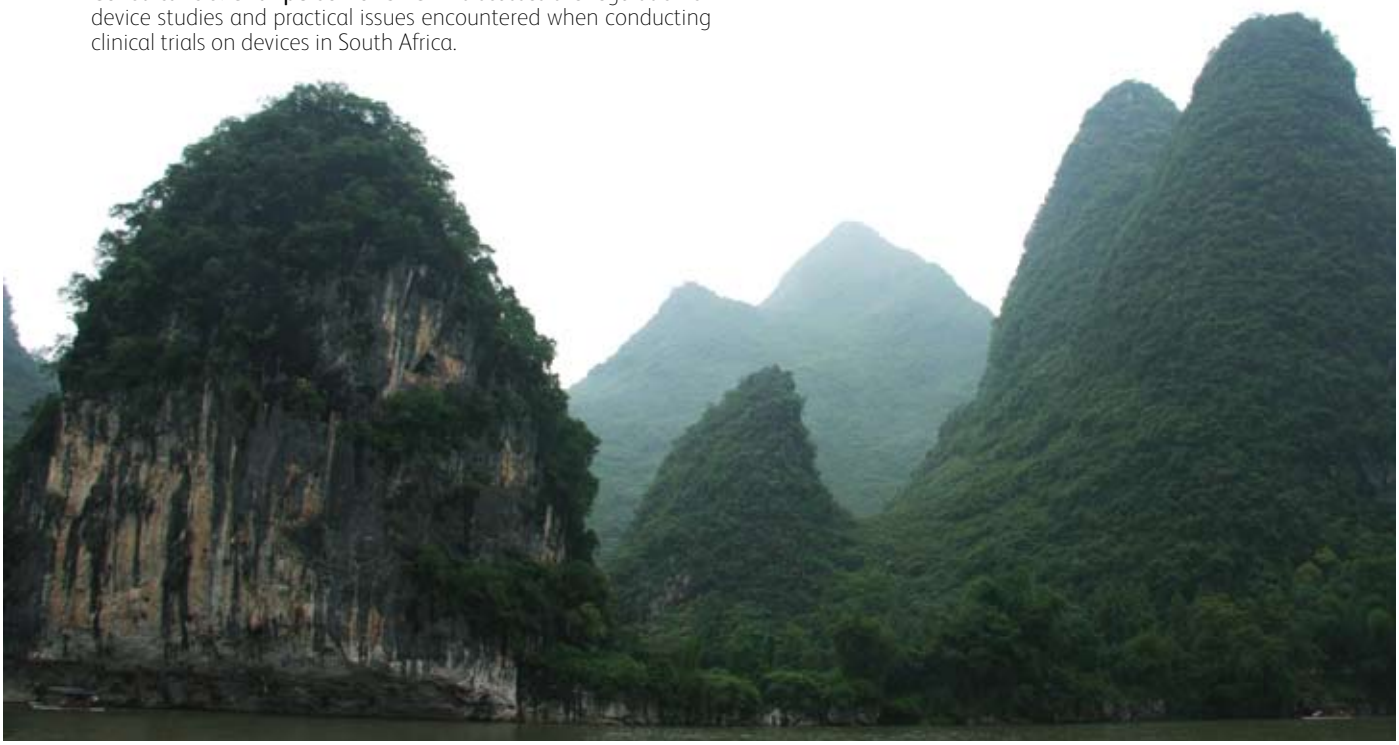

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Publisher's Note

We have reached the end of 2009, and what a year it has been. I think we are all going to look back at 2009 and notice that the world has changed. We are all looking at the broader picture. From US, India & China pledging to reduce Carbon Emissions to the Pharmaceutical Industries endeavouring to find cure for many forgotten diseases, and diseases still prevalent in many developing countries, I think we will make this into a better world. When we launched Journal For Clinical Studies in 2008, we wanted to encourage Sponsors & CROs alike to venture out and utilise the vast pool of treatment naive population in the world, to find cure for diseases, and make health care available to all.

We wish to thank all our readers, contributors and advertisers for the enthusiasm with which the Journal for Clinical Studies has been welcomed and adopted as a must read journal. We would especially like to thank our editorial advisory board for the dedication and commitment they have given to this unique journal, and sourcing out information that are crucial to the modern drug discovery and development world.

In this latest issue we bring you another selection of valuable information.

Trends in Clinical Trials and CT Supply Management – what happened in 2009, what may be expected in 2010 is an area covered by Dr Claudio Lorck of Temmler AG. While Walter Chalkley of Thomson Reuters writes on The FDA-EMEA Good Clinical Practice Initiative and the need to harmonise and eliminate duplicate activities.

Russell Neal focuses on how Australia and New Zealand offer proven solutions for helping SMEs with exciting novel products, While Francine Hakim of Caribbean Clinical Research Associate writes on the need for a good solid community education campaign to educate local communities, where clinical trials are being introduced for the first time into a region.

Eastern Europe and the Baltic regions are relative new comers in the Clinical Trials field. Dr Janis Skards of Documeds provides a quick guide on what is happening in these newer European economies. Dr. Xunting Zeng of INCROM CHINA looks in to the important developments in China, the compilation of the Pharmacopoeia of China (2010 Edition) and the issue of the Regulation for National Essential Drugs List.

The Korea Food and Drug Administration released a report on approval status of clinical trials in Korea last July, and Do Hyun Cho of KHIDI looks into this issue. Our India Watch, is on "The glorious metamorphosis: Compelling reasons for doing clinical research in India" is a joint initiative by FICCI and Ernst & Young, and is an outstanding initiative to portray the clinical research landscape in India.

Dr. Ranya Shahrouri of ClinArt analyses Jordan for the first time in JCS and Francis P. Crawley of GCP Alliance examines China.

Stephen Gunnigle of Kinapse looks at ways in which clinical trials can be run more effectively. The hot topic of Pharmacovigilance is explained by Sanjay Motivaras of 4G Pharmacovigilance, especially with new medicinal products

Dr. Nermeen Varawalla, President & CEO of ECCRO gives you a detailed overview of DIA Clinical Forum, Nice 2009: Improving Clinical Development Together.

Heinrich Klech, CEO of Vienna School of Clinical Research reflects on improving people's skills in Emerging Countries while Kohei Wada of Daiichi Sankyo, Co Ltd & JPMA representative of ICH Steering Committee explains the Role of the ICH-GCG (Global Cooperation Group) in facilitating the roll-out of ICH in non-ICH regions and countries.

We have a focus on South Africa where Dr Lynn Katsoulis, Chairperson of SACRA discusses the regulation of device studies and practical issues encountered when conducting clinical trials on devices in South Africa.

Dr Patricia Lobo interviews Dr. Dave Clark of Aurum Institute for Health Research on THIBELA a preventive study into TB in the gold mining industry, and finally Dr Jessica Trusler of BARC explains how various partnerships will define a new reality for Africa's disease burden and a legacy of good health for its people.

We wish you all happy holiday season and see you in January 2010. "**Happy New Year!**"

HELLO

I am Karl M. Eckl,

In 2000, we specialised in the type of Phase I and IIa Clinical Studies which are critical and often delay clinical development because of difficult recruitment conditions. These studies are:

- PK studies in the target population (e.g. Oncology Patients)
- PK studies in patient populations used as pharmacological models like patients with renal and hepatic impairment
- Proof of Concept studies in the target population (phase IIa) to speed up strategic decisions in clinical development of new medicinal products

Why are these studies so difficult to perform?

- No therapeutic benefit for patients increase reluctance to participate in such a study.Therefore it is necessary to have a panel of such patients whenever possible.
- Reproducible boundary conditions are difficult to achieve in normal hospital settings. Therefore our own clinical sites are exclusively used for clinical research.

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The FDA-EMEA Good Clinical Practice Initiative

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) are required to ensure that clinical studies submitted in support of Marketing Authorization Applications (MAAs) in the EU, and New Drug Applications (NDAs)/Biologics License Applications (BLAs) in the US, have been undertaken in accordance with good clinical practice (GCP), and that ethical standards have been maintained no matter where the studies took place. That requirement has strained the inspection capabilities of the EMEA and FDA in light of the growing globalization of clinical development coupled with the current worldwide economic slowdown. The ultimate result of these limitations being that only a sampling of the clinical development sites is being inspected.

In an effort to eliminate duplicate activities, harmonize similar inspections procedures, and to insure that clinical trials are conducted in an appropriate, uniform manner internationally, the FDA and EMEA have undertaken the FDA-EMEA GCP Initiative. This initiative is a collaborative effort to inspect more clinical trial sites for products that are intended to be marketed in both regulatory regions.[1]

The agencies have identified three chief aims of the initiative:[2]

- To conduct periodic information exchanges on GCP-related information. These exchanges will serve not only to better enable the exchange of GCP inspection planning information, but will enable the agencies to better select sites/studies for inspection and report inspection outcomes.

- To conduct collaborative GCP inspections. This objective will be met through direct cooperation in conducting inspections. Sponsors assist in this aspect of the process through advance notification to EU and US regulators of any joint marketing authorizations planned for both regions.
- To share information on interpretation of GCP. This information includes the timely notification of new GCP-related legislation and other related regulatory documents.

The initiative began officially on September 1, 2009 with an 18-month pilot phase that will focus specifically on products regulated by the FDA's Center for Drug Evaluation and Research (CDER) and the EMEA. Following the conclusion of the pilot phase the two agencies will assess the performance and success of the initial inspections, and the process will be modified if needed.

This initiative is the outgrowth of recent measures taken by both regulatory bodies regarding the standardization of clinical trials across international borders. Precursor measures taken by the individual agencies include:

- The 2008 FDA revision of the guidance "Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application" which better defines the standards under which the agency will accept data from foreign clinical trials in support of domestic applications and submissions.[3]

- The 2008 EMEA strategy paper entitled "Acceptance of Clinical Trials Conducted in Third Countries, for Evaluation in Marketing Authorization Applications" which increased emphasis on the ethical standards required of clinical trials conducted in third countries.[4]

The new FDA-EMEA GCP Initiative marks a progressive step from these measures towards the global standardization of the regulations applicable to drug product development. The aim of all the regulatory measures is the adoption of GCP as the "gold standard" for clinical development worldwide. ■

References:

1. Public Notice: EMEA-FDA GCP Initiative, July 31, 2009. Available at: http://www.emea.europa.eu/pdfs/general/direct/internationalcoop/EMEA_FDA_GCP_Initiative_2009.pdf.

2. News Release: FDA, European Medicines Agency Launch Good Clinical Practices Initiative, August 3, 2009. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm174983.htm.

3. Federal Register: April 28, 2008. Volume 73, Number 82, 22800-22816.

4. "Acceptance of Clinical Trials Conducted in Third Countries, for Evaluation in Marketing Authorisation Applications." Available at: http://www.emea.europa.eu/Inspections/docs/22806708en.pdf

Walter Chalkley, RAC, is a senior editorial project manager for IDRAC, *a regulatory affairs information database and part of Thomson Reuters Scientific. His education was completed primarily at Virginia Commonwealth University in Richmond, Virginia. He has been with IDRAC for nearly six years.*
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Australasia Watch Nov 2009

What an interesting year 2009 has been. International politics, financial crises and some of the wildest weather we have seen for some years; it has certainly been a difficult environment for most industries. Traditionally the biopharmaceutical and medical device industry has been considered somewhat recession-proof – after all, we all get ill and therefore demand for new and effective treatments will always remain high. It seems that this time around, we as an industry have been more sensitive to this current recession/global financial crisis (GFC) than in the past, with greater difficulty in finding funding proving the core issue for many SMEs around the world.

Many readers will be familiar with Australia's propensity for bush fires. They are devastating in their fury, are indiscriminate, and unfortunately there are innocent victims. Such fires are not however a new phenomenon and indeed, in Australian ecology are actually essential for new life, with many seeds requiring a fire in order to germinate. It seems that destruction of the undergrowth above ground, the clearing of competition if you like, reduces the hurdles for new shoots to quite literally spring forth. Aboriginals, as Australia's native land managers, have long used bush fires as a tool for getting rid of the deadwood and stimulating new and stronger growth so as to provide new food sources, both flora and fauna. So what does traditional land management have to do with clinical research? Looking back at 2009, I wonder if the GFC and all the turmoil seen in the last 12-18 months might be seen as our economy's, and indeed our industry's, land management tool, and drive our product development to a new phase of revitalised growth.

As Journal for Clinical Studies is the voice of the emerging clinical research markets, you won't be surprised if I also suggest that now more than ever this is the time for emerging regions to take stock of our respective points of difference, such as regulatory efficiency, cost-effectiveness, and a motivated, high-quality researcher community, and get better at educating the international community. In this way developers, both large and small, might mitigate some of their ongoing financial challenges by finding better clinical solutions available in emerging clinical research countries. Australia and New Zealand, as I have previously espoused in these pages, offer a proven solution for helping SMEs with exciting novel products.

Looking forward therefore to 2010, I would like to wish all emerging markets success and encourage you to take advantage, and demonstrate globally that there is some blue sky in our countries that could be good for those new and exciting therapies, those new shoots after the fire storm. ■

Russell Neal *has almost 20 years' experience in the healthcare industry. He moved with Quintiles UK to Sydney in 1994 before moving to Singapore in 1999. In 2003, Russell returned to Australia following three years as a Regional Training Manager Asia Pacific and is currently Chief Operating Officer at Clinical Network Services (CNS).*
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Caribbean Watch - Part 2

When bringing clinical trials into a region that has not previously had the opportunity to participate in clinical trials, knowledge of less than favourable past experiences attached to clinical research projects can give rise to the 'guinea pig syndrome', where there are concerns with community response, community acceptance and community participation. Without subjects no clinical trial can be successful.

We have been working in the Federation of St. Kitts and Nevis on a Phase II athlete's foot project, where we can now confidently make certain conclusions about the success rate for subject recruitment and retention, and community acceptance and response.

A good solid community education campaign to educate the local community as to how far clinical trials have come over the years, an informed consent process, and publicity regarding the benefits of participating as a subject in a clinical trial have all been exceptionally helpful.

With the advent of cable television in even the most rural areas, and many of the channels coming from major cities in the US and the UK, advertisements are often seen by people from areas other than those where the clinical trials are being conducted. Indeed, these same advertisements are being seen even in remote areas of the world, including the Caribbean.

With the world becoming smaller and lifestyles more alike, one reason for the successful development of clinical research trials in the Caribbean is the influence of cable television, and exposure to advertisements encouraging participation in clinical research trials. With this information being brought into the homes of people who would not necessarily be exposed to an invitation to participate in a clinical trial, it means that local advertisements will sound similar to what has been brought to their attention via another medium from a society where that type of advertisement is common, and which has sparked an interest.

"one reason for the successful development of clinical research trials in the Caribbean is the influence of cable television"

Avenues of recruitment that have shown results in the Caribbean are local radio talk/call-in community radio shows, local print advertisements and educational articles about clinical research and active projects, flier distribution at job fairs and health fairs, and word of mouth.

Another area of concern is subject retention. Again, from our experience recently we can say that subject enrolment was met within the forecasted timeframe, and even exceeded anticipated response; subject compliance was exceptional; and subject retention was 100%. There were none lost to follow-up and no withdrawals of consent, and subjects expressed an interest in seeing more projects like the one currently being conducted in their primary area of interest to Caribbean subjects, whether it be diabetes, cholesterol, hypertension and women's health.

Upcoming issues will look at shipping and receiving of study supplies, government concessions on duty of study supplies, and branching out in the Caribbean. ■

Francine Hakim, BS, CCRA *is the president and founder of Caribbean Clinical Research Associates, LLC, a consortium of physicians and health care professionals conducting clinical trials serving the Caribbean. CCRA assists with logistics for timely approvals and clean study conduct. CCRA keeps a pulse on the research activities and thought leaders of the region. Its principal, Ms Hakim has 15 years experience in the pharmaceutical research industry in business development, project management, full scope of site monitoring, auditing, training and lecturing. If you are interested in learning how your next trial will be conducted in the Caribbean.*

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China Watch

New Developments in Clinical Trial Regulations in 2009

The last several issues introduced registration of imported drugs, the new-drug monitoring period, regulations on clinical trial design and so on. In the present article, we will talk about the latest developments in clinical trial regulations in China in 2009.

Two of the most remarkable events in the medicine field are the compilation of the Pharmacopoeia of China (2010 Edition) and the issue of the Regulation for National Essential Drugs List.

1. The compilation of the Pharmacopoeia of China (2010 Edition), which will come into force on July 1, 2010, has been finished. It is also the ninth edition of the Pharmacopoeia since the foundation of China, and will be published in three volumes: Traditional Chinese Medicines (Volume 1), Chemical Drugs (Volume 2) and Biological Products (Volume 3). There are more than 4600 monographs of drugs and other articles in the Pharmacopoeia 2010 Edition, with 1300 new admissions in comparison with the 2005 Edition. The monographs in the 2010 Pharmacopoeia cover almost all the varieties that were indicated in the National Essential Drug List and the Drug Catalogue of National Basic Medical Insurance.

2. A videophone conference launching and deploying the works of national essential drugs system has been held by the State Council's Advisory Group of Healthcare Reform on August 18 2009. Measures for Establishing National Essential Drugs System, Regulation for National Essential Drugs List (Interim), and National Essential Drugs List (Part of Distributed for Primary Medical and Health Organizations Use) (2009 Edition) were issued. The National Essential Drugs List (Part of Distributed for Primary Medical and Health Organizations Use) (2009 Edition), which will come into force on September 21, 2009, consists of three parts: chemical drugs and biological products, traditional Chinese medicine products, and prepared slices of Chinese crude drugs. The chemical drugs and biological products are classified according to clinical pharmacology, 205 kinds in total, while the traditional Chinese medicine products are classified according to the function, 102 kinds in total. Meanwhile, in order to strengthen administration on national essential drugs and ensure the national essential drugs quality, SFDA formulated the Provisions for Strengthening Administration on National Essential Drug Quality according to the Drug Administration Law of China and the Regulations for Implementation of the Drug Administration Law of China.

In addition, five regulations relative to drug clinical trials have been opened for public opinion by SFDA as follows:

1. In order to strengthen the conduct of ethics review in clinical trials and safeguard the rights, safety, and wellbeing of all trial subjects practically, SFDA drafted the Guideline for Ethics Review of IRB in Clinical Trials.

2. In order to strengthen the supervision on drug clinical study, SFDA drafted the Standard for the Qualification Check of Drug Clinical Trials Institution.

3. SFDA formulated the revised draft of Provision on Medical Device Registration for responding to practical requests. The last revision was in 2004.

4. SFDA issued the revised draft of Good Manufacturing Practice (GMP) for enhancing the supervision of drug manufacturing. The existing GMP is the second edition, revised in 1998.

5. In order to ensure the supervision of the drug side effects report and monitoring, Measures for the Administration on Report and Monitoring of Drug Side Effect revised draft was issued by SFDA. The existing regulation is the second edition revised in 2004. ■

Dr. Xunting Zeng *has decades of experience in the field of Clinical Trials. Dr. Zeng received his PhD at Kansai Medical University, Osaka, Japan, since then he worked as Special Investigator at International Medical Centre of Japan. Later he joined InCROM Group, a Japan based leading international Contract Research Organization firm. Dr. Zeng is currently General Manager of InCROM China and heading up to elevate China clinical trial with global standard.*

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Estonia

• According to SAM statistics the increase in the number of trials has been slowed down. Having peaked in 2007 (93 applications), there were only 83 applications in 2008 (the same level as 2004). The limits in terms of quantity have probably been achieved. However, this may not be the case for each speciality, as the distribution of the trials among the different specialities is quite diverse. According to 2008 data the leading specialties, with 9-11 trials, were neurology, endocrinology and psychiatry, while dermatology, ophthalmology, as well as rheumatology were represented with quite modest numbers.

• In January 2009, the CTA review timelines were decreased from 60 to 30 days for Phase II-IV trials. Considering the possibility of parallel submission to EC and CA, there are prerequisites for shortening considerably the overall preparation phase of the clinical trials (http://www.ravimiamet.ee).

Latvia

• From 1st October 2009, under the framework of reorganisation of governmental institutions, the State Agency of Medicines (SAM) of Latvia has taken over responsibility for registration and authorisation of clinical studies, and vigilance of medicinal devices (http://www.zva.gov.lv/doc_upl/011009_jaunas_fjas_no_vsmtva_v2.pdf)

• From 15th January 2009, according to the implementation of Pediatric Regulation EC 1901/2006, clause 8, the SAM of Latvia requests new MAA or variations with the data from Pediatric Investigational Plan (PIP) or EMEA-authorised deferral.

• According to the annual SAM report in 2008 in Latvia, 87 de novo applications for clinical studies (in 2007 there were 88), in 11 SAM meetings. Four out of 88 authorisations were in pediatrics. 251 studies were ongoing (235 in 2007) (Annual SAM report 2006).

Lithuania

• On 8th of April 2009 the Decree of the Minister of Health No.V-262 amending Decree No. V-435 ("Concerning the confirmation of requirements of clinical trials, conduct and quality assurance") was implemented in order to improve authorisation for clinical trials on medicinal products conducted with a pediatric population. Decree No. V-262 implemented a few new requirements applicable to source documents.

• A new edition of Law on Legal Protection of Personal Data of the Republic of Lithuania became effective on the 1st of January 2009, defining new requirements for personal data protection in biomedical research (www.vvkt.gov.lt)

Ukraine

• The regulatory base for clinical studies in Ukraine has implemented EU Directives 2001/20/EC, 2001/83/EC and 2003/94/EC) from 13th February 2009 (http://www.pharma-center.kiev.ua/view/en/new_doc).

• Directive #95 from 16th February 2009 "Good clinical practice" was issued by MoH. This document establishes general requirements for planning, organising and conducting clinical studies. This document was adjusted in accordance with CPMP/ICH/135/95 (E 6) "Note for Guidance on Good Clinical Practice", 2002 (CPMP/ICH/135/95 (E 6).

• The number of clinical studies in Ukraine has a tendency to increase (36 in 2000, and close to 200 in 2008). Analysis of trials in the aspect of medicine sectors shows activity in the following fields:

- Oncology – 56
- Psychiatry – 37
- Cardiology – 28
- Asthma – 14
- RA – 12
- Thrombosis – 11
- Diabetes – 10

Russia

• According to the national Association of Clinical Research Organizations, from January to July 2009, 242 clinical studies were running, of which 155 were international multi-centre ones (http://acto-russia.org). Nevertheless, during the second quarter of 2009 a 17% decrease over the corresponding period of the previous year has been reported (www.synrg-pharma.com).

• New guidelines/recommendations for safety reporting in clinical studies are going to be developed and implemented (www.roszdravnadzor.ru). Currently the federal standard for Good Clinical practice (Gost R 52379-2005) must be followed.

• On 23rd and 24th November 2009 in Moscow, the International Conference of Standardization of Medicinal Products and Harmonization of Requirements will be held by the Federal Service on Surveillance in Healthcare and Social Development (RosZdravNadzor) and the European Directorate for Quality of Medicines and Healthcare (EDQM) (http://acto-russia.org)

• The Central Ethics Committee by RosZdravNadzor (RZN) has authorised the national company Microgen to perform a clinical study with a vaccine against A/H1N1 flu virus (http://cra-club.ru)

• The average timescale for regulatory approvals has decreased in Russia from 148 days in 2007 to 132 days in 2008

• Starting from October this year, there is a new procedure for safety information submission to the Ministry of Health - all safety information (CIOMS, IND Reports etc) should be submitted to competent authorities via a new online electronic system. ■

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The Glorious Metamorphosis - Compelling Reasons for Doing Clinical Research in India

(Study conducted jointly by Federation of Indian Chambers of Commerce & Industry (FICCI) and Ernst & Young)

Clinical research is a true multinational, multibillion, multidisciplinary industry. The clinical research industry has grown around the world at an unparalleled rate in the past few years. It has opened up new vistas of employment and business opportunities for a large number of people.

Various surveys also support the fact that India is one of the most attractive destinations for clinical trials, with robust growth of 31 % per annum over the last four years. India now participates in over 7 % of all global Phase III and 3.2 % of global Phase II trials.

The study "The glorious metamorphosis: Compelling reasons for doing clinical research in India" is a joint initiative by FICCI and Ernst & Young, and is an outstanding initiative to portray the clinical research landscape in India. The study aims to present the reasons for the shifting clinical trial footprints towards emerging markets, the role of India as an emerging market, and an assessment of the capabilities and potentials for growth of the Indian clinical research industry. The study explores India's inherent strengths and the core value proposition it offers across the clinical research value chain.

The clinical trial segment (Phases I-IV) is valued at USD42 billion, which constitutes almost 65 % of global clinical research expenditure. Longer clinical trials are required with higher patient enrolment rates for complex therapies like oncology, CNS, endocrinology and cardiovascular diseases. These therapeutical areas account for 68 % of total clinical trial protocols. But with the global slowdown affecting both the pharmaceutical and the biotechnology industries, these industries are forced to consolidate, downsize and offshore their clinical trials operations to low cost countries. Thus, the emerging markets are becoming preferred destinations for the conduct of clinical trials. Amongst the emerging markets for clinical trials India is ranked third and has the fastest growing number of Phase II-III sites.

- Scientific feasibility
- Medical infrastructure
- Clinical trial experience
- Policy regulations and public investment
- Commercialisation potential
- Cost competitiveness

Scientific Feasibility

Patient pool: India has approximately 32 million patients in urban areas and 72 million patients in rural areas at any given point of time. The patient pool consists of both treatment-naïve patients, and those with a high standard of care. India's patient mix mirrors the global drug development pipeline and it is expected that nearly 15-20 % of the global patient enrolment for key therapies will be from India. As a result, India has one of the fastest subject recruitment rates.

Medical Infrastructure

India's medical infrastructure, both public and private, is speedily gearing up to provide the necessary enabling environment for smooth clinical trial conduct. India has approximately 42,500 private hospitals, 7000 government hospitals, 942,000 hospital beds, 14,000 diagnostics labs & 290 medical colleges. More and more hospitals are enrolling for the accreditation programmes.

Clinical Trial Experience

India has an inbuilt infrastructure for conducting clinical trials. The key constituents of a clinical trial ecosystem are:

- GCP-compliant sites
- Human resource expertise
- Ethics committee
- Site management organisations
- Central labs
- CROs and captive centres

Since 2004, the number of clinical trials conducted in India has grown from 40 to over 350. India is ranked 12th globally in the number of sponsored Phase II-III clinical trial sites.

Policy Regulations and Public Investments

India's regulatory environment has undergone significant change in the last few years. The Indian Council of Medical Research and Director General of Health Services provide guidance and a regulatory framework for clinical research in India.

Schedule Y of the Drug & Cosmetics Act 1940 governs clinical research in India. Schedule Y was thoroughly reviewed and amended in January 2005.

CDSCO (Central Drugs Standard Control Organization), which regulates the industry, has continuously been taking initiatives aimed at improving the governance and compliance culture, such as streamlining and reducing the timeframes of approval, enhancing monitoring, oversights and enforcement, e-governance, and creating the environment for micro-dosing and Phase I studies. CDSCO is headed by the Drug Controller General of India. At the state level, the State Food & Drug Administration Department controls clinical research conducted under its jurisdiction.

Commercialisation Potential

The Indian Pharmaceutical Industry is expected to triple to USD20 billion by 2015 from USD7.1billion in 2007. This would move India into the world's top 10 in market share terms. This commercial attractiveness of India is a key factor influencing India's attractiveness as a clinical trial destination.

Cost Competitiveness

In addition to the factors mentioned above, India offers significant cost competitiveness in the conduct of clinical trials, including infrastructure, operational, patient recruitment, drug, manpower, data management and processing cost.

	India	US
CRA	USD 40-55/hr	USD 120-150/hr
Project Manager	USD 50-60/hr	USD 160-180/hr

Table 1: Hourly rate comparison of India and the US.

Allied services in clinical research like clinical data management, pharmacovigilance, medical writing and biostatistics are the cornerstone of successful drug development and regulatory approval. India has emerged as an attractive destination for offshoring clinical trial allied services. The Indian allied service market is growing at a compound annual growth rate of 21% as compared to 7.5% globally. There are more than 40 companies in India which offer one or more allied services. India offers a significant cost advantage to service providers and sponsors.

Charge-out rate (USD/Hr)	India	Developed economies
Data entry operator	USD 10-20	USD 30-50
Biostatistician	USD 30-70	USD 100-150
Medical writing professional	USD 30-70	USD 100-150
Pharmacovigilance professional	USD 50-100	USD 140-150

Table 2: Shows that India has significant cost advantages as compared to developed economies

Moreover, the government permits Foreign Direct Investment on an automatic basis. Investment in the clinical research sector is under the automatic route (i.e. without any ceiling on foreign investment and Government approval). The Government also permits foreign technical collaborations.

All the above advantages position India as one of the most attractive destinations to conduct clinical trials globally. ■

Reference: *The glorious metamorphosis - Compelling reasons for doing clinical research in India – http://www.ey.com/IN/en/Industries/Pharmaceutical - Study conducted jointly by Federation of Indian Chambers of Commerce & Industry (FICCI) and Ernst & Young.*

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Clinical trials in Korea: Approval status of 2009 and forecast

The Korea Food and Drug Administration released a report on approval status of clinical trials in Korea last July. The report shows that KFDA approved a total of 169 trials for the first half of the year 2009 (January 1st-June 30th), which is ten times larger in number in comparison to the 31 cases in the whole of the year 1999.

Clinical trials approval applications submitted by local pharmaceutical companies (87 cases) slightly outnumbered those submitted by global companies (82 cases), and the top 13 companies were shown as conducting 48% of the total clinical trials.

Still the Phase III studies form the largest portion of clinical trials operated in Korea (36%) compared to Phase I and II trials which accounted for 25% and 18% respectively. Nevertheless, Korea made dramatic enhancements in quality, showing a remarkable increase in the early phase trials from the Phase III trials, which used to be the dominant studies conducted in Korea.

Looking at therapeutic areas, oncology, cardiovascular and CNS trials accounted for 2/3 of all trials conducted in Korea, which indicates that trials conducted in Korea very much reflect worldwide new drug development trends, and also shows westernised disease patterns in Korea.

Most of the multinational companies' oncology clinical trials are intensively focused on early stage studies, which is understood by the high levels of trust which global companies have in Korean investigators and clinical centres. Breast cancer, lung cancer and liver cancer are the most conducted anti-cancer studies in Korean clinical trial centres.

KFDA's IND (Investigational New Drug Application) approval status report showed that clinical trials conducted in Korea have similar patterns and share common trends with those of advanced nations in terms of therapeutic areas and portion of trial stages being conducted.

Korea's rapid growth in the area of clinical trials is the result of public private partnerships to enhance the competitiveness of clinical trials, and is also very dependent upon quality of research infrastructures and advanced human resources.

Clinical trials conducted in Korea next year are estimated to increase by approximately 28%, the average increase in the last five years. Also, the expansion of government-managed local clinical trial centres from 12 sites to 15 sites this year will strengthen the competence of Korean investigators.

Since the total market size of clinical trials worldwide is 40 billion USD, and Korea has about 2% of the total market share, there still is a long way to go for the Korean medical community to be a global leader in clinical trials. ■

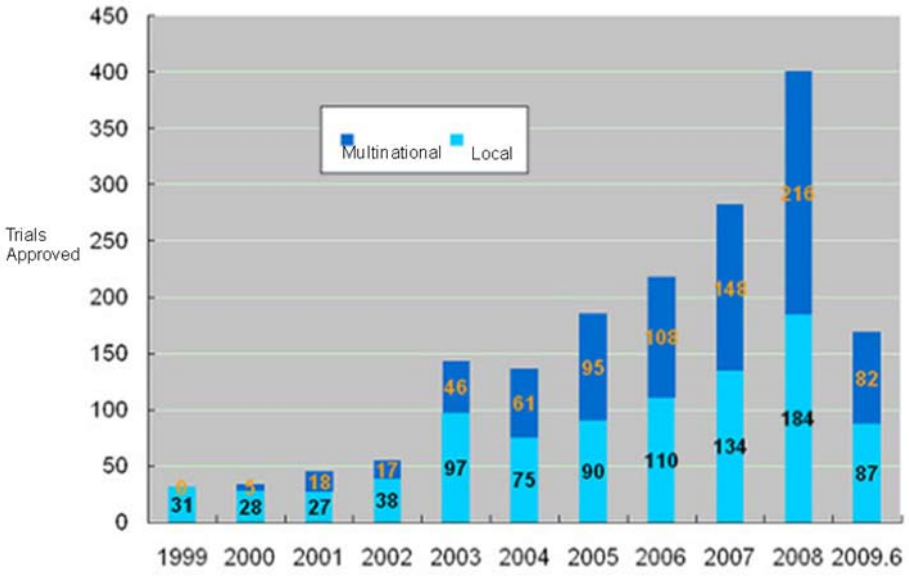

Table: 1 Number of approved clinical trials: KFDA, 2009

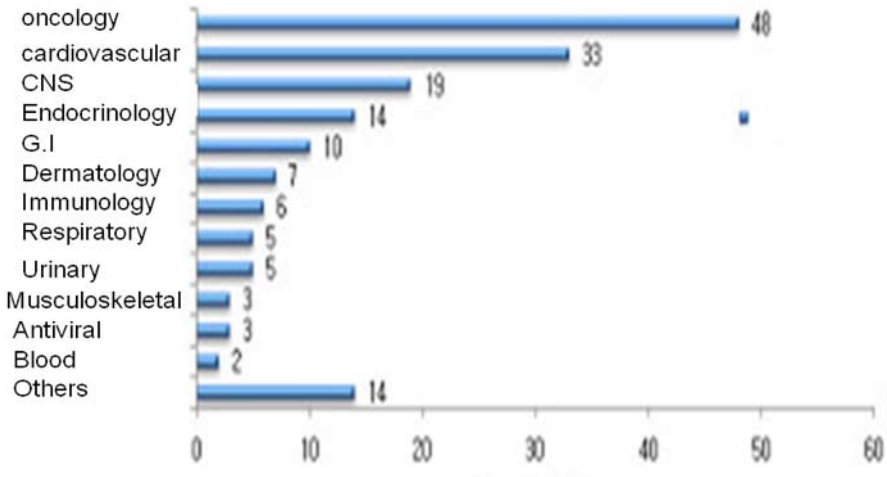

Table: 2 Number of approved trials by therapeutic areas: KFDA, 2009

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"Jordan First"

Being a sign of medical progression and a civilised nation, clinical research is on the top of the agenda of medical stakeholders in Jordan who are aiming to secure funds for clinical research. On the other hand, pharmaceutical companies are willing to invest in excellent clinical trials centres. Most clinical trials centres view the future for conducting quality clinical trials and accreditation in following international standards such as ICH GCP, FDA Guidelines or WHO Guidelines.

Taking Jordan as an example, the Jordanian regulatory authorities some time ago adopted international standards in conducting clinical trials. From the regulatory affairs point of view, Jordan is a rich soil for excellent clinical trials where the government has set regulations which are to be followed in both private and governmental hospitals. Moreover, major hospitals or educational hospitals have their own local research ethics committees.

Jordan is a good place for clinical studies because the maximum cost of the study reaches around half the cost in European countries or the US. This is because of low taxes and a competitive cost base in terms of operating costs, plant costs, and development and labour costs. Research ethics committee approval can be obtained in one month. Investigators are highly motivated to take on clinical trials, and are aware of GCP and protocol compliance. Moreover, the availability of investigators with expertise in most medical disciplines is an advantage that Jordan has to offer. Furthermore, the physician-patient relationship is strong, facilitating the recruitment process where the physician can allocate large populations for a particular disease area in a short period of time, and can keep patients committed to follow up.

The flexibility of amending laws and regulations in accordance with the private sector has made Jordan a mature environment for conducting modern business. Moreover, Jordan is one of the first countries to sign a free trade agreement with USA, has joined the WTO, and has a trade pact with the EU. Trade-related intellectual property rights have soothed sponsors' as well as researchers' fears, and consequently will attract investments and funds for R&D and technological development. Jordan has various other advantages, such as strong human and educational resources, a stable and positive image, and international auditing standards.

Funding for clinical trials can be either local or foreign. Locally raised funds are directed in most cases to investigate epidemic diseases or to fill the gap for urgent research that investigates the community's most contagious diseases. As a foreign company, establishing clinical research in another country will bring high risks, such as mastering the regulatory process, the need to monitor the progress of the study, and the most important, bridging the cultural gap. The roles of clinical research organisations are crucial in connecting west to east, while foreign investors are interested in our region but facing the regulatory lack of information. This is where an experienced clinical research organisation can assist in solving local mysteries for interested foreign companies. The clinical research organisation will be local and can operate perfectly within the region, and they can manage the research locally from A to Z. It is good to note that the Middle East has many clinical research organisations that follow international standards in conducting clinical trials.

Having all these advantages, Jordan is a perfect place for clinical research among the Middle Eastern countries. The opportunities for clinical research are substantial, physicians are eager to investigate, costs are notably low, and there are vast resources coupled with a high standard of regulations: the clinical research future should be bright in Jordan. ■

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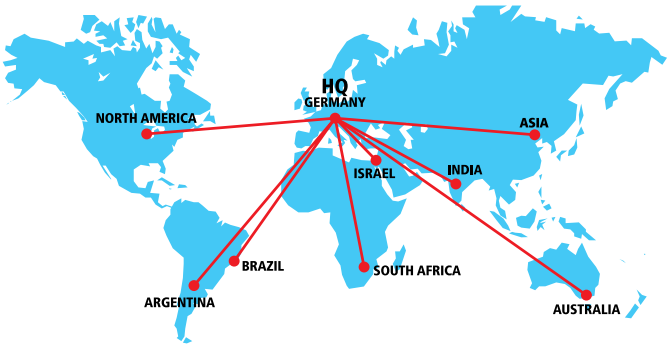

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Trends in Clinical Trials and CT Supply Management – what happened in 2009, what may be expected in 2010

Among several new regulatory developments observed in 2009, the following have been selected due to their relevance also for clinical trial management activities occurring outside the European Union. An important document with relevance for outsourcing and contracting clinical trial supply activities is expected for 2010.

1. What happened in 2009

A draft revision of the "Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial" was submitted for public consultation. This draft revision of the existing detailed guidance aims at:

- Incorporating changes to the legislative framework (inter alia, paediatrics, advanced therapies); and

- Clarifying and further harmonising the requirements of format and content of the request for authorisation, substantial amendment, and declaration of end of the clinical trial.

The draft revised document was submitted for public consultation in June 2009, with contributions having been invited from all stakeholders related to clinical trials, including stakeholders who are not established within the European Union, by September 08, 2009 at the latest. (http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2009/2009_06/2009_06_11-publicconsultation.pdf)

In March 2009, a CONCEPT PAPER ON REVISION OF THE EU GUIDELINE ON GOOD DISTRIBUTION PRACTICE (GDP) was published. As today's distribution network for medicinal products and investigational medicinal products has become increasingly complex and involves many players which are not necessarily wholesale distributors as defined in Directive 2001/83/EC, and has been subject to total or partial outsourcing, harmonisation and improvements of GDP requirements need to be developed and incorporated into the GDP Guideline. A number of areas have been identified, such as supplier qualification, "counterfeit" medicinal products, obligations for traders, procedure for inspection of wholesale distributors, qualifications and training of GDP inspectors, format of an inspection report and of a wholesaler's authorisation etc.

The "Questions and Answers document" in the EudraLex volume 10 on clinical trials has been revised (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/2009_07_28-q%26a_v4.pdf), with two new questions being added:

- The first new question answered in the document is that authorised medicinal products used as a comparator do fall under the definition of an IMP, if "…they play a fully equivalent, symmetric, role as counterparts to the tested products, and this from the inception of the protocol to the interpretation of the study results. The comparator is an IMP and the conditions (circuit, traceability and accountability methods) under which the comparator is used are to be strictly the same as those of the tested product."

- The second new question answered is that a study is a "non-interventional trial" if the medicinal product is prescribed in full compliance with the marketing authorisation, the patient is not treated according to a pre-defined trial protocol, and no additional diagnostic or monitoring procedures are applied to the patient.

2. What may be expected for 2010

While outsourcing and contracting of GMP regulated activities other than operations traditionally considered as manufacture and analysis in supplying clinical trials is a continuous growing alternative to doing it in-house, the rules for contracting and auditing are considered necessary to be adapted. In the EU, currently chapter 7 of the EU GMP guide defines the GMP frame for contract manufacture and analytics. Processes considered by the GMP/GDP Inspectors working group, GMP/GDP IWG not being sufficiently covered by chapter 7 are:

- Qualification and validation work for new premises
- Maintenance and calibration of equipment and premises
- Storage and distribution
- Artwork generation and print ready material
- Assessment and sourcing of starting and packaging materials
- QP and other professional services such as GMP audits of suppliers
- Washing and depyrogenation and/or sterilisation of packaging materials used in manufacture
- Hosting of IT functions
- Document archiving and storage

The current concept paper (http://www.emea.europa.eu/Inspections/docs/64867809en.pdf) proposes a draft proposal for review by the GMDP IWG being available by May 2010, anticipating the start of consultation to be achieved by September 2010, and the finalised guideline being available by September 2011 for adoption by the Commission. ■

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Improving Clinical Site Productivity

Abstract

There are a number of factors in the industry that make clinical trials more costly, more time-consuming and requiring more patients than in previous years. More than ever, sponsor companies are being pushed to deliver clinical trials quicker and more cost-effectively. The purpose of this paper is to look at ways in which clinical trials can be run more effectively and thus improve productivity. The paper introduces the Kinapse Clinical Site Productivity Framework as a mechanism to evaluate seven key areas in the patient recruitment process. By assessing each key area, issues can be identified and prioritised, and solutions designed and improvements made.

Introduction

In 2005, there were twice as many patients required for a new Phase II study than there had been in 2001[1]. New and inexperienced sites were needed to identify and recruit these additional patients, incurring greater costs for the study. In an internal Pfizer analysis of the clinical studies it conducted from 2000 to 2006, the Director of Clinical Trial Recruitment Services found that 80 % of the participants in Pfizer studies were enrolled by 26 % of the participating clinical sites[2]. In addition, 8 % of sites failed to complete a single patient[2]. Schultz et al. (2007) similarly reported that 254 out of approximately 2000 clinical sites also failed to recruit a single patient[3]. In a recent assessment within a leading specialty pharmaceutical company performed by Kinapse in 2007, those sites which failed to enroll one patient ranged from 0 % to 8 % depending on the specific study assessed4. In addition, increasing the number of countries used in studies often delivers fewer patients per country and drives up costs and complexity[4]. Costs are also impacted by delays during study start-up, maintenance and close-out phases.

"increasing the number of countries used in studies often delivers fewer patients per country and drives up costs and complexity"

Cause of Delay	% Cited
Contract and budget negotiation and approval	47 %
Patient recruitment and enrolment	42 %
Availability of study drug	41 %
Ethics Committee review and approval	40 %
Investigator selection	39 %
Correction of case report form enquiries	38 %
Protocol development and refinement	37 %
Legal review	36 %

Table 1: Explanations given for delays in clinical trials in the European region1.

Improving clinical site productivity within a global pharmaceutical or biotechnology company is much more complex than is first apparent. The complexity is compounded by a number of factors not limited to the execution of the clinical study at site. It is commonly thought that high quality support from a Clinical Research Associate (CRA), a strong trust-based relationship with the investigator and site staff and the proactive support of the sponsor organisation will be enough to deliver the necessary patient numbers at the regional and global level. However, this is not the case. It is also imperative that resources are invested early in protocol development to ensure that the protocol is deliverable and the right countries and sites are selected to participate in these studies so as to prevent, or at least limit, delays to timelines (Table 1).

The paper will examine the critical relationship between the Clinical Development and Clinical Operations functions and will introduce the Kinapse Clinical Site Productivity Framework (Figure 1) as a mechanism to identify process improvements which will impact clinical site productivity[3]. This framework, which is discussed in detail below, aims to provide a basis for the effective delivery of patients into a clinical study in a more productive manner than is often employed.

Description of Framework

1. Protocol Feasibility

Central to the delivery of a clinical study is a robust protocol written collaboratively between the medical function responsible for the development of the protocol synopsis, and those representatives of the clinical operations function who will be given the responsibility for executing the clinical study. Excellence in medical science and the development of an innovative protocol provides the opportunity for patient stratification or data which will

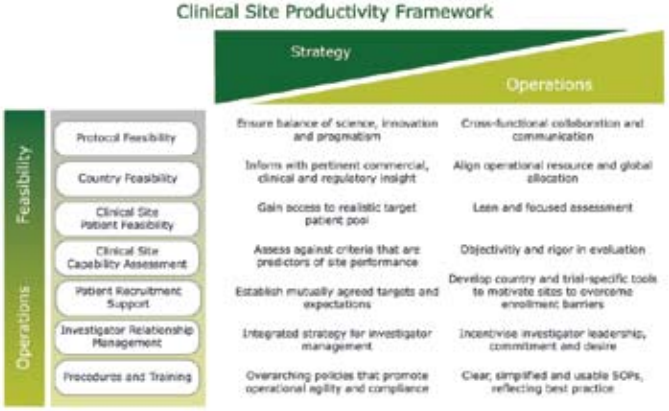

Figure 1: The Kinapse Clinical Site Productivity Framework

support a strong regulatory submission.

The input from experienced operational colleagues early in protocol development, in an advisory capacity, enables these innovations to be grounded in the real world practicalities of executing a clinical study within the primary or secondary care setting. This interface between the medical function and the clinical operations function can be challenging, and unless company culture reinforces a collaborative approach through appropriate objectives and measures for the individual and the team, the resultant protocol may be difficult to execute to time, cost and the necessary quality.

2. Country Feasibility

Relevant, up-to-date information from a commercial, clinical and regulatory perspective is critical to support effective decision-making. A challenge here, particularly outside of the US, is that this knowledge resides at the country or sub-country level and without a clear, timely and routine process for delivering information between the countries, the regions and the global level, important data which may impact regional or country selection may be unavailable, not up-to-date or used to its full potential.

Most pharmaceutical companies operate a feasibility process which requests either regions or countries to provide a provisional patient commitment and cost for completion of the study within a given timescale. The source and accuracy of this information is often country-dependent, whether this is an existing or new therapy area to the country. Sources for this type of information range from user-friendly, real-time global databases, local investigator databases in Microsoft Access, commercially available databases, clinical research networks, clinical site feasibility questionnaires/interviews through to the opinion, experience and knowledge of a clinical project manager within the country. Critical to this process is the reinforcement of good behaviours, rewarding individuals and the country-level organisation for the accuracy of forecasting patients, costs and timelines. Poorly devised metrics can contribute to bad behaviours with countries provisionally committing low numbers of patients to ensure that their targets are always met, however, an overall low provisional patient commitment collated at the global level requires additional countries and clinical sites to be approached, resulting in an increased overall cost per patient for the study.

3. Clinical Site Patient Feasibility

Depending on the pharmaceutical company, the term clinical site feasibility can have different meanings. In some, this is a general term which describes the entire process of setting up a clinical site, the period from receipt of a finalised protocol within the country through to a site initiation meeting. This all-in-one approach to the pre-study phase can lead to ambiguity, unfocused effort and wasted time and cost, as it makes the assumption from the start that every investigator site will be included in the study.

In contrast, we advocate a staged approach, with the initial stage focusing on how many patients the clinical sites within a country can deliver in terms of patients/site within a time period, and if each has access to specific, technical equipment necessary to conduct the study in question. Only once this has been assessed would a more detailed capability assessment occur (see point 4). This approach quickly identifies the provisional inclusion of the site in a study and informs the country-level forecast or commitment (as described in the previous section).

4. Clinical Site Capability Assessment

Once the country has been selected to take part in a study, there needs to be a robust assessment of each provisional investigator site to determine qualification or selection to be involved in the study, which is the next stage gate. The purpose is to derive a thorough understanding of the capability of the investigator site and to inform decision-making around its selection or exclusion from the study. Examples of criteria to be assessed are included in Table 2.

Organisations benefit from a robust and routine process as this focuses the time during the assessment and over time through experience and familiarity. Critical to this approach is the need to only procure information relating to the selection or exclusion of the site from the study. This lean approach is time-efficient during the assessment and also reduces the complexity and time associated with the actual decision to select or exclude. In addition, for investigators and clinical sites which are currently working with the sponsor or have just completed a study, information relating to site capability will be readily available and negates the need to conduct a formal assessment at the site, which also adds to efficiency gains.

1. R&D Office (contract, procedures, timelines, financials)	10. General and specialist equipment availability
2. Ethics committee meeting dates and deadlines for submission	11. Investigator eligibility to receive and dispense Investigational Medicinal Products (IMPs)
3. Principal investigator experience within the specific indication	12. Medical license and expiration dates for the Principal and sub-investigators
4. Clinical site staff experience of involvement in clinical research	13. Time commitment expectations during monitoring visits
5. Pharmacy assessment and experience	14. Source data and access during monitoring, audits and inspections (as applicable)
6. Review of Principal Investigator and other site staff CVs to determine appropriate medical knowledge, experience, Good Clinical Practice (GCP) and patient confidentiality training	15. Motivation and enthusiasm of investigator and site staff to be involved in this specific investigation
7. Dedicated coordinating research nurse	16. Inspection findings, serious breach (UK) associated with the clinical site
8. Specialist departments e.g. pathology's availability to process samples in accordance with the protocol	17. Dedicated workspace, IT connectivity during monitoring visits
9. Knowledge and ability to do electronic data capture (EDC)	18. Awareness of ongoing competitive studies and their recruitment close-out dates

Table 2: Clinical Site Capability Assessment

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Are you looking for a dedicated research team?

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- MENE is operating in Middle East and Europe and furthermore a member of Research Point Global. This membership enables MENE to conduct clinical studies globally

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5. Patient Recruitment Support

Sponsor support to staff involved in patient recruitment is often critical to achieving patient numbers within a desired timeframe. The sponsor has a number of opportunities to provide this support and an optimal mix should be defined for a particular study. These include providing education directly to the patient through clear and understandable patient information sheets and newsletters, and identifying support networks in their locality. When an organisation is embarking on a study in an unfamiliar therapeutic area (TA) or indication, the use of clinical research networks also provides the opportunity to identify new patients.

Support to clinical site staff, such as nurses, may include teleconferences with other sites to share best practice and training in finding and consenting patients, as well as creating awareness of the study within the broader care facility. A more creative way, which involves greater time input and cost to the sponsor, is the development of study-specific websites to generate awareness and to keep patients in touch with the status of the study. There are a number of successful engagements reported by companies such as Rapid Trials who focus specifically on the investigator site and supporting recruitment, often under challenging circumstances. In addition to the specific activities, the building of rapport and the natural development of the relationship with the site staff can be motivational in itself, for both sponsor and clinical site staff.

6. Investigator Relationship Management

A focus of activities at the local operating country level is the effective management of the relationship with investigators. There are a number of roles that may be involved in this relationship and these benefit from coordination on behalf of the sponsor company. Sponsor company staff need clarity of role and responsibilities in order to manage the investigator effectively, and there is unlikely to be a "one size fits all" approach which can be applied to a pharmaceutical company due to their differing sizes, organisational structures and cultures. That being said it is relatively easy to map relationship management responsibilities at each step of the process, be it investigator meetings, monitoring visits or motivational visits.

Sponsor organisations benefit from moving away from a transactional approach to the relationship with the investigator and the broader clinical site, approaching the relationship as a trust-based partnership. In a competitive market-place, where investigators can choose or prioritise the sponsor companies he/she works with, it is important to invest time in the relationship to ensure that the partnership is a rewarding experience for the investigator and clinical site staff.

Investigator needs must be understood and met. Investigator perceptions of a sponsor company and its requirements can be obtained by a number of mechanisms including subscribing to an industry-wide survey such as that provided through CenterWatch, commissioning a survey from within the sponsor company, focus groups (representing a cross-section of investigators), one-to-one interviews and, more informally, feedback from investigator-facing staff. Through investment in these types of approaches a sponsor company will be able to reflect on the relative success of its investigator management tactics, identify unmet investigator needs and opportunities for improvement. Justification for the investment in investigator relationship management should be sought through improvements in recruitment numbers, timelines and quality. Indeed these data can also influence the decision of an investigator to take part in a future clinical study.

7. Procedures and Training

The interpretation of what a good GCP-compliant procedure is differs between pharmaceutical organisations and is often influenced by the strength of regional versus global organisational culture. In addition, in an attempt to be all-encompassing, these procedural requirements can often be large and unwieldy. Whilst it is difficult to proscribe how an organisation should structure its document hierarchy e.g. policies, standard operating procedures, work instructions etc., it is important to clearly articulate roles and responsibilities within a procedural document. Focused procedures which are written clearly, simply and in a logical, stepwise manner and reflecting current best practice within the organisation are beneficial to the reader.

The CRA is increasingly becoming the major investigator-facing representative of a pharmaceutical organisation during the execution of a clinical trial. Investment in training (TA, indication, protocol, negotiating and influencing, communication, project management and GCP compliance) is not an insignificant cost to a sponsor. Whereas an organisation must provide and document certain compliance training and that TA/disease area (DA) and protocol training continues to occur through the study team network, at times of economic uncertainty and cost control it is often the "softer skills" budget which is under the greatest scrutiny and pressure. New CRAs or those undergoing refresher training also benefit from training provided by individuals more experienced in their role, mentoring, co-monitoring visits and the opportunity to discuss challenges they face with their peers.

Conclusion

Pharmaceutical and biotechnology companies are under ever-increasing pressures to cost-effectively recruit patients to clinical studies at a time of increasing ethical, regulatory and contractual scrutiny. Speed needs to be balanced with quality and the time available for patient recruitment maximised through the timely conclusion of contracting and budgeting negotiations in addition to regulatory and ethics submissions during the study start-up phase.

The Kinapse Clinical Site Productivity Framework (Figure 1) provides a mechanism to evaluate seven key areas in the study recruitment process and, by assessing each using lean tools and techniques, the sponsor can quickly identify and prioritise issues and design and implement solutions to the same. Whereas interventions in one area can achieve improvements, it is only through the holistic assessment of the end-to-end process, with internal and external stakeholders, that the patient recruitment process can be fully optimised and clinical productivity improved. ■

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Pharmacovigilance - Post Marketing

The concept of pharmacovigilance is not new; however, the area within the pharmaceutical industry is relatively recent in comparison to other disciplines.

Although the concept of monitoring the safety of marketed medicines has been with us since the 1960s, at the beginning of the decade few people outside France used the word 'pharmacovigilance'. In recent years, however, the field has moved on and acquired itself a new name.[3]

Put simply 'pharmacovigilance' as defined by the World Health Organization (WHO) is "the pharmacological science and activities relating to the detection, assessment, understanding and prevention of adverse events of drugs, biologics and other medicinal products, or any other possible product-related problems".

Pharmacovigilance is particularly concerned with adverse drug reactions, which are officially described as: "A response to a drug which is noxious and unintended, and which occurs at doses normally used… for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function".

It can be argued that pharmacovigilance is a surveillance method designed to prevent a company losing profit because of adverse effects when so much investment has gone into creating the latest blockbuster drug, but in truth it is a means to identify early detection and prevention of unexpected and avoidable harm to patients from medicines, the management of risk and therapy improvement.

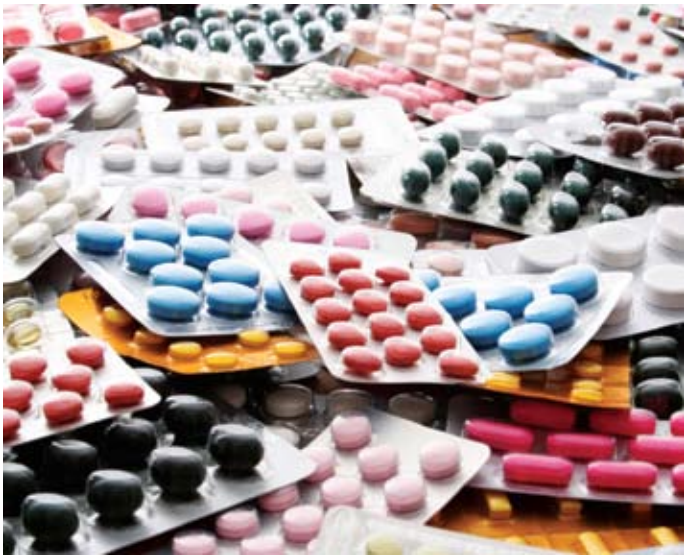
Pharmacovigilance is becoming seen as a more important part of a product's life cycle, and the limits and inhibitory factors which were seen to hinder its progress in the past - such as it being seen as an under-resourced function and being subject to cautious bureaucratic - processes[1] are being addressed. However these challenges and others are still being observed.

"Pharmacovigilance is now seen as an integral part of clinical research, a function that is present from clinical trials through to post-marketing surveillance."

Pharmacovigilance is now seen as an integral part of clinical research, a function that is present from clinical trials through to post-marketing surveillance.

This is because although clinical trials may identify certain adverse drug reactions, the pool of patients upon which the drug is trialled is not sufficient to provide enough data about its safety and efficacy, hence monitoring the safety after clinical trials is just as important in identifying further information about the drug's safety profile.

With high profile drug withdrawals within recent years, regulatory authorities have been forced to increase their vigilance of medicinal products emerging from companies in the public eye, resulting in major losses in revenue. This in turn has resulted in companies fighting back by increasing their surveillance efforts through more robust methods, starting from stage 1 in the product's life all the way through to the product being marketed, in order to identify real and potential risks. These methods employed include continuous signal detection and risk minimisation strategies, but more ingenious methods are being developed on a daily basis in an effort to safeguard public health and the perception of a safe medicinal product.



With this proactive change in pharmacovigilance from being a compliance-led discipline to one which focuses on productivity, it has evolved from being a function which companies "had no choice but to have" into one having a strategic value for the safety profile of a product[4].

Whilst pharmacovigilance is seen as a major issue within Europe and the USA, the emerging markets such as Japan and India are now proactively expressing an interest in pharmacovigilance and are working to thus improve their operations. Reasons for this could be that the practice of reporting adverse drug reactions to pharmaceutical companies is on the rise due to increased public education which then in turn encourages authorities to follow suit, and thus increase the chances of more adverse reactions being identified globally.

Various studies conducted globally show that experiencing an adverse effect to a drug affects the quality of life of the patient, which

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therefore may result in an increase in patient hospitalisation, and furthermore may result in patient death. A meta-analysis conducted in 1998 estimated that in the United States 106,000 hospital patients died from an adverse drug reaction. Thus, adverse drug reactions may rank from the fourth to sixth leading cause of death[2].

It is therefore in the pharmaceutical company's best interests to try to prevent adverse events occurring to their products.

Although companies are becoming more proactive in these efforts, the global economic crisis has resulted in companies becoming concerned about processing reports while keeping costs to a minimum.

It is fair to say that challenges have developed because of the increased pressures imposed on companies. Companies are increasingly finding it hard to find suitably qualified staff who are experienced in various aspects of pharmacovigilance, since larger companies have got into the habit of having staff who specialise in specific areas of pharmacovigilance, which in turn provides challenges in obtaining a sufficient headcount with reduced budgets.

Because of the greater emphasis of drug surveillance, various methods have been introduced by the regulators to keep the emphasis of patient safety at the forefront of pharmacovigilance. In recent times this has been achieved through mandatory electronic reporting of adverse events to the regulatory authorities, pharmacovigilance inspections in order to ensure that company methods of pharmacovigilance are acceptable and that a company's pharmacovigilance obligations are being met, risk management planning and specifications to identify known and potential safety issues and missing information about safety, the continuous submission of periodic safety reports, and in some cases risk management plans as well.

In addition, regulatory authorities have further enforced drug safety and its surveillance through the introduction of legislation, such as within Europe the Clinical Trials Directive and "the requirements for pharmacovigilance systems monitoring of compliance and pharmacovigilance inspections" (volume 9A of the rules governing medicinal products in the European Union).

Organisations involved in drafting recommendations include the Council of International Organizations of Medical sciences (CIOMS) along with the World Health Organization[5].

Recommendations from the CIOMS working groups are often used as the basis for guidelines by the International Conference on Harmonization of Technical requirements for Registration of Pharmaceuticals for Human Use (ICH).

It seems that once a solution is found for one challenge, another appears.

How do we tackle all this? In the past few years, guidance documents like volume 9A and FDA guidance have been released, in addition to the ICH guidelines on safety. In addition to that, authorities such as the Medicines Healthcare and Regulatory Authority (MHRA) published a book on good pharmacovigilance practice[6]. In addition to authorities providing guidance, various articles have also been produced attempting to provide views on how to ensure that pharmacovigilance and issues surrounding the discipline are tackled competently.

With more and more guidance being provided, companies are beginning to turn to external service providers to carry out their pharmacovigilance obligations. This practice is cheaper than in-house pharmacovigilance, as it reduces fixed costs along with ensuring vast levels of pharmacovigilance expertise in many of the outsourcing companies used; but it also results in an area still not seen as a core business area being separated. Also, by outsourcing pharmacovigilance, the company is not obliged to stick to one provider, thus allowing the companies to have all aspects of pharmacovigilance covered from clinical trials through to post-marketing surveillance.

As Dr Biswas stated: "Pharmacovigilance is not easy, and its errors and problems are repeated. Of course, by proactively detecting signals and with better risk management plans, some of the questions may be answered. However, without proper educational training in this field and good work experience it is difficult to understand the intricacies that are involved and what to look for".

Further, as the Erice manifesto had mentioned nearly three years ago, "pharmacovigilance cannot progress into the next decade by gesture politics, short-term compromise or bureaucratic concession; it demands transformation of focus, attitudes and goals and the profound commitment of all players to the single ambition of putting patients' safety, needs, wishes and priorities at the very centre of the global drug safety enterprise; it requires vision, resources, investment, continuous advocacy and local and international champions"[1].

Pharmacovigilance over the next decade will once again evolve, with more risk strategies being tested and more regulation being put in place as the pharmaceutical world ventures into new areas of medicinal product creation. Only time will tell if the current efforts are sufficient, or whether companies will have to further invest into this area, and how the current global economic crisis will be a governing factor in the future of pharmacovigilance. ■

"Pharmacovigilance over the next decade will once again evolve, with more risk strategies being tested and more regulation being put in place as the pharmaceutical world ventures into new areas of medicinal product creation"

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DIA Clinical Forum, Nice 2009: Improving Clinical Development Together

Close to 400 delegates with an interest in clinical research attended the 3rd Annual DIA Clinical Forum at the Acropolis Conference Centre located in the centre of the charming city of Nice, France, from the 19th to 21st October, 2009. Clinical research professionals working for large and small biopharmaceutical companies, CROs, specialist vendors, regulatory agencies, investigative sites and academia formed the conference attendee list. In keeping with the tradition of the DIA Clinical Forum, DIA Special Interest Area Communities focused on Clinical Data Management, IT/Validation, Medical Information and Communication, Statistics and Medical Writing held their annual meetings within the umbrella of this conference. Thus each of these specialities was well represented along with those engaged in clinical operations. This mix of participants constituted an engaged forum able to collectively reflect on and discuss the conference theme, "Improving Clinical Development Together."

"The trick is to deploy technology to serve the clinical research process instead of clinical research becoming a slave to technology."

Programme Overview

As Ingrid Klingmann, Chairperson of the Conference Programme Committee noted, the conference theme, "Improving Clinical Development Together" responds to the need for "bundling forces, sharing knowledge and experience and creating practical ideas together, in these challenging times for drug development." In keeping with this objective the programme strongly featured case studies, success stories and best practices with a practical and operational flavour. The main two-day conference programme was structured along seven tracks, which included the Special Interest Area Communities described above along with Clinical Operations, Post Marketing Development, Drug Safety and Quality Assurance. Each of these tracks featured six to eight sessions, each typically including three speakers assembled to discuss cutting edge topics. This programme structure was successful in enabling attendees to focus on their special interest areas, as well as "dip into" other tracks to learn the latest thinking on subjects lateral to their focus areas.

A description of each of key tracks is briefly summarised:

Clinical Operations, Post Marketing Development, Drug Safety and Quality Assurance

This theme included a wide range of sessions ranging from Personalised Medicine and Gene Based Therapy to Outsourcing and Large Post Authorisation Studies. The session on "How to manage Recruitment in Difficult settings and indications" had speakers representing a global CRO, PharmaNet; a pharmaceutical company that specialises in niche, rare indication, Genzyme and a communications company, Fast4wD Ogilvy. They shared their experiences with recruiting clinical trial subjects in challenging conditions, namely paediatric populations, patients with rare diseases and in highly competitive indications, whilst the session on "Delivering the Expected Value from Global Clinical Trials" sought to raise the understanding of the challenges of globalisation of clinical development and help craft initiatives to improve its process and outcome. Here Dennis Joseph, Area Head of Clinical Operations, Pfizer described an initiative to reduce the number of countries included within their international clinical trials by selecting only those that met well-defined criteria, such as population size, clinical trial approval timelines and data quality standards. John Norrie, Professor of Biostatistics at Glasgow University, highlighted the importance of training and support at the investigative site, describing their experience with the adaptation of UK training modules for a developing world environment. Lastly, Olga Nedok-Bigelow, Senior Medical Director, ICON Clinical Research, shared her experiences and the department's practices with providing 24-hour medical monitoring for global clinical trials.

Clinical Data Management

The two sessions on Leading Technologies were well attended both by data management professionals and generalists seeking an update on Electronic Data Capture (EDC) and related tools. These sessions highlighted that "paper is history", with new technologies being developed and introduced at an increasingly rapid frequency. The trick is to deploy technology to serve the clinical research process instead of clinical research becoming a slave to technology. The eClinical tools examined included EDC, SMS, Digital Pen and personal PDAs. Further,

Bombay events will mark India's growing power in global pharma

Early December brings the staging in Mumbai of the third CPhI India and second P-MEC India pharma ingredients, services and technologies event. A combined total of over 600 exhibitors from over 80 countries are expected at the Bombay Exhibition Centre for the 2009 events – including two key conferences - being held on 1 – 3 December.

The events take place against the background of gathering evidence for India's acceleration as a major player across the whole range of global pharma services. The combined and well-established exhibitions are the largest pharma services event in India and South Asia and have become an industry "must attend" networking event since the inaugural CPhI India, back in 2006.

The exhibitions are free of charge and pre-registration is via www.cphi-india.com.

The Bombay events come at an exciting time for the Indian pharma community. Despite the recent global slowdown, Indian pharma has maintained standout growth rates, with a sector forecast to quadruple, from US $6.3bn. in 2005 to US $25bn. in 2015.

In their report this Summer – and underlining the important addition this year of the ICSE India contract services event - E&Y/OPPI (Ernst & Young/Organisation of Pharmaceutical Producers of India - OPPI) noted that India's outsourcing sector is growing at 43 %, with drug discovery and development segment growing at 65 % - well over three times the global average. India is targeting to become one of the top five innovator countries by 2020, discovering one out of every 5 – 10 drugs discovered worldwide.

In addition to high quality exhibitors, the 2009 events include two new launches. Joining the debut of ICSE India, BioPh India will focus on the convergence of technologies and business models in pharma and healthcare biotechnology – especially across the common interest areas of innovation, product development, clinical trials, manufacturing and supply logistics.

The co-located additions of BioPh India and ICSE India to CPhI India and P-MEC India add impressive further depth and networking value to the combined events.

Growth will figure strongly in the major conferences complementing the exhibitions. These begin with the Indian Pharma Summit on Wednesday 30 November, addressing the issues, opportunities and challenges for India as an emerging global pharma hub.

Under the title: "The future of India Pharma – India Pharma Vision 2020", the event will identify opportunities and challenges and create a roadmap to achieve consistent growth of India as a destination for pharma research, development and manufacturing.

The Summit will be inaugurated by the President of India, Pratibhatai Patil. Organisers are the Government of India's new Department of Pharmaceuticals and UBM India Pvt. Ltd. Venue is the Mumbai Grand Hyatt. Registration is via: www.indiapharmasumit.com

Secondly, and staged alongside the first two days of CPhI India, in the BioPh pavilion at the Bombay Exhibition Centre, Biosimilars India 2009 will cover a wide range of topics in 17 sessions across three half-day modules.

"India is now moving towards centrestage in world pharma, with its overall pharma market growing at better than 9 % - and key segments much faster. CPhI and the co-located events are the natural meeting point that enables a high level of networking and business development across the academic, development, R&D, services and manufacturing communities", said CPhI India Event Director Annemieke Timmers.

"With the BioPh India and ICSE India launches and a strong conference programme adding to a high level of pre-registrations, all our indications are that this year in Mumbai will see our strongest Indian events so far", added ICSE, BioPh and P-MEC Event Director Haf Cennydd.

Key industry organisations supporting the exhibitions will include Pharmexcil – the Government of India's pharmaceutical export promotion council; the Indian Drug Manufacturers Association (IDMA); the Organisation of Pharmaceutical Producers of India (OPPI); the Bulk Drug Manufacturers Association (India) (BDMA); the Indian Pharma Machinery Manufacturers Association (IPMMA) and the Indian Analytical Instruments Association (IAIA).

The events are jointly organised by UBM International Media and sister company UBM India Pvt. Ltd.. Breaking UBM launch show records on its debut in 2006, CPhI India became the fourth member of the brand's global event "family" and was joined by P-MEC India in 2007.

UBM International Media's annual sister events for the pharma ingredients and services sector include Worldwide (Europe – October); Japan (April); China (June); and South America (August). For websites, see: www.wherepharmameets.com; www.cphi-india.com; www.pmec-india.com and www.bioph-online.com .

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ways to integrate multiple technologies whilst maintaining flexibility as well as user-friendliness was discussed, referring to a range of case studies and best practices. The session on Data Quality discussed statistical and procedural methods to define, generate and measure data quality. The role of centralised monitoring in maximising data quality for minimal cost in a multi-centre randomised clinical trial was presented, followed by a description of achieving database quality in the field of pharmaco-epidemiology. Finally, the track included a lively panel discussion on "CDM: Focus on the Future" moderated by Nick Lucas, Head of Global Data Management at INC Research.

IT/Validation

In the complex healthcare information landscape, interoperability of standards is essential for the seamless flow of information between care-givers, clinical trial sponsors, CROs and regulators. Organisations like CDISC, HL7, IHE and SAFE have become the main enablers of healthcare information integration. Two sessions on Standards, chaired by Pierre-Yves Lastic, Senior Director, Data Privacy and Healthcare Interoperability and Standards, and Valdo Arnera, General Manager Europe, PHT Corporation, examined the evolving impact of CDISC and HL7 on data management, regulatory submissions and pharmacovigilance, the contributions of SAFE-BioPharma, IHE and CDISC to improve drug safety reporting and the international harmonisation of healthcare information standards.

Medical Information and Communication

This track, chaired by Janet Davies, Director, International Medical Information, Gliead Sciences, began with a very well attended session on Medical Information Collaboration in Europe, which presented the current status of the Medical Information community in Europe; namely, professionals working in Medical Information, Medical Communication and Medical Affairs. Feedback from the 2008 survey of Medical Information professionals in Europe and from the recent US workshop was presented. Approaches to change and re-shape medical information departments so as to make pharmaceutical companies better suited for the pressures they face were presented in the form of case studies by representatives from Pfizer, AstraZeneca and GlaxoSmithKline. The balance between the benefits and risks of providing medical information to patients is a point of much debate. This was addressed by a presentation on the European regulations relating to pharmaceutical packaging that set the scene for a discussion on the challenges of communicating with patients. Further, interacting with healthcare professionals was reviewed using case studies related to follow-up letters for reported adverse events. Metrics to evaluate and benchmark the consistency and quality of outputs from Medical Information departments and the deployment of technology for knowledge management were topics that were also covered by this lively track.

"Approaches to change and re-shape medical information departments so as to make pharmaceutical companies better suited for the pressures they face were presented in the form of case studies by representatives from Pfizer, AstraZeneca and GlaxoSmithKline."

Statistics

The Statistics track, jointly chaired by Francois Aubin, Medical and Methodology Director, Cardinal Systems and David Wright, Senior Statistical Assessor, MHRA, showcased some of the recent developments in pharmaceutical statistics. These included updates on regulatory guidelines related to bioequivalence and missing data, methodological challenges with using pre-clinical information in the drug development process and statistical issues with safety data. Case studies demonstrating innovations in modelling and simulations as applied to early and late stage studies were presented by representatives from Vifor Pharma Ltd, F. Hoffmann-La-Roche and the University of Warwick's Health Science Research Institute. A joint session with the Medical Writing track examined Clinical Trial Disclosure. The demand for communicating clinical trial information, including trial design and results, on publicly accessible websites is growing. The challenge is to provide accurate information which is never misleading and is consistent with scientific publications and regulatory submissions. Best practices to meet these challenges were shared by presenters from EMEA, Roche Products and Novo Nordisk.

Medical Writing

Efficient and timely preparation of ICH E3 compliant clinical study reports, outsourcing of pharmacovigilance writing, preparation of Paediatric Investigational Plans and best practices for publishing clinical data were some of the topics examined by the Medical Writing track. Mary Gardner Stewart, Divisional Director, Lundbeck, chaired a session on Global Strategies in Medical Writing which examined methods to prepare Marketing Authorisation Applications (MAAs) for multi-country studies. In spite of ICH and the concept of a Common Technical Document, the EU, Japan and the US have different requirements for their MAAs dependent on what data were collected and where. Presentations exploring ways to plan global development programmes, the incorporation of bridging strategies and deciding on the content of MAAs provided attendees with ideas to address these issues which will only increase with the heightening globalisation of drug development.

CRO Delivery is a Myth

The plenary session of the DIA Clinical Forum is usually a debate

conducted in traditional style with invited speakers proposing and opposing the motion and voting by members of the audience. The title for the 2009 debate was provocatively selected to be "This House Believes that CRO Delivery is a Myth". This title, relevant to the conference theme of "Improving Clinical Development Together", set the stage for CROs and sponsors to debate why the sponsor-vendor relationship can be fraught with frustrations instead of being an effective partnership. The debate was expertly chaired by Julianne Hull, Senior Director, Pfizer. The debaters proposing the motion were Andy Parrett, Medimmune and Chairman of the Pharmaceutical Contract Management Group, and Jens Reinhold, Head of Non-Interventional Studies at Bayer Schering, who described their numerous disappointments with CROs that failed to adhere to pre-agreed budgets and timelines. Jorgen Seldrup, Senior Statistician, Quintiles, and Nermeen Varawalla, President, ECCRO, opposed the motion, claiming that by their nature clinical trial projects were unpredictable and uncertain; a reflection of the complexities of global clinical trial conduct, hence attributing the blame for unexpected outcomes to CROs was unfair. Dr Varawalla reminded the house that it was CROs who have led the way in innovating and developing improved clinical development processes, resources and technologies; whilst making them flexible and robust enough to deal with both complexity and unpredictability which have become the hallmarks of present drug development. Both sides agreed about the need for more strategic and trusting partnerships with vendors and explored more effective models for vendor alliances. In response to questions from the audience it was emphasised that expertise related to products was firmly within the domain of sponsor companies, whilst that related to clinical development processes was in the realm of CROs. Based on the audience votes, which were counted both before and after the speeches and discussion, the opposition was victorious by a comfortable margin. The plenary session which was attended by about 200 delegates proved to be successful in generating an engaged discussion over an important but contentious subject.

Next Meeting

Given the valuable role that the annual DIA Clinical Forum plays in bringing together clinical research professionals engaged in all key disciplines at an European venue, to discuss the latest drug development thinking and operational practices, this conference is certain to grow in popularity and impact. The 2010 DIA Clinical Forum will be held in Lisbon, Portugal between 11th and 13th October. Do mark your diaries!

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The key to fostering medical development and innovation is investment in people's skills

The world is getting smaller. Clinical research has become widespread in emerging countries. The reasons are obvious: large, often treatment-naïve patient populations, faster recruitment of patients, potential for cost savings, motivated investigators, fewer competitor trials, high growth markets of tomorrow, opportunity to study diseases of the developing world, etc (1). As a matter of fact the number of clinical trials included in submissions to the USFDA has risen from 15 % in 1998 to 40 % in 2008, and is expected to rise by over 2/3 by 2012 (2).

Emerging countries have responded increasingly to this momentum, and have used various methods to address the regulatory, governance and ethical needs in relation to the performance of clinical trials in their countries. In parallel with this, the major regulatory bodies such as USFDA and EMEA have put together regulations which give more specific guidance under which the data generated by human clinical trials can be accepted and included in drug submissions (3,4).

However, there are still multiple challenges facing this fast-growing "business" of clinical trials in emerging geographies. Despite many professional organisations from the developed world including big pharma and, more extensively, global, regional and local CROs having increased their presence in these markets, there is still only a thin cover of well-trained and experienced researchers from the academic side, as well as experienced clinical research professionals from non-academic institutions. The demand forces the need for education and training for clinical research professionals, mainly for the rapidly-growing emerging markets like India and China, followed by Latin America, CEE and Africa. Whereas in the developed world clinical trial staff are characterised mainly by personnel who are active in clinical research, in the emerging markets staff are recruited from graduates and postgraduates in medicine, pharmacy and other scientific disciplines without experience in clinical trials. As a consequence, human research managers have a challenge to recruit and develop the manpower or to hire experienced professionals.

The programmes for education and training in clinical research offered by the various providers today are pretty variable. Many organisations today offer such programmes. They range from university-based course programmes down to simple introductory short courses, mainly on good clinical practice (GCP). The university-based courses usually offer well-structured and broad-ranged tuition in clinical research, with good opportunities for further specialisation. They usually provide accreditation, CME credits, and in some cases even a masters degree in clinical research. Many providers offer e-learning tools for selected topics. Larger pharma companies also offer courses for their own personnel, but here the trend is to outsource those activities.

University-based programmes intentionally target the academic audience, such as clinical physicians in academic institutions, or physicians or researchers in pharma companies. Their programmes are on a broad basis usually and offer virtually all elements of education and training for clinical research professionals. They include intense education on GCP, on regulations of major regulatory bodies and related national authorities. Advanced courses also cover all specific and pragmatic aspects of the ethical backgrounds, including their historic elements. All major aspects need to be addressed, such as ethical review board submissions, informed consent process, protocol review, information and evaluation, project management, budget preparation, regulatory submissions, management and recording of adverse events, study drug accountability and setting up one`s research site.

Some of the academic providers, such as the Vienna School of Clinical Research (www.vscr.at), a non-profit academic institution which collaborates with 15 international universities, offer additional specialised courses for researchers such as advanced biostatistics and publication workshops, as well as therapeutic area-specific protocol development workshops. VSCR is active in many emerging markets, and since the year 2000 has trained more than 4000 research professionals from more than 90 countries. VSCR also offers a masters degree programme through the Vienna Medical University (MUW).

Academic accreditation and quality control in courses in clinical research are of rising importance because of the need for increasing quality in emerging geographies. Because of the lack of experienced staff, the mandate of high quality training and education is an essential and critical success factor for a sustainable and ethically sound growth of clinical research in emerging markets, and will have a high potential impact for the credibility of data obtained from these parts of the world. Audits and inspections from regulatory bodies focus increasingly on the quality of training and education of the research personnel involved (1).

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Similar to the services of VSCR, there are other organisations in training and education in Europe or the US who are either of direct academic origin or have close links to academic institutions providing accreditation, CME credits or even academic degrees. These include the Institute of Clinical Research, UK (www.icr-global.org) and the European Center for Pharmaceutical Medicine, Basel, CH (www.ecpm.ch). Recently the European Union and EFPIA have announced that they will jointly sponsor a large, comprehensive programme in the next five years, entitled the Innovative Medicines Initiative (IMI), with the aim of improving the competitiveness of the European pharmaceutical industry. One of the projects (Pharmaceutical Medicine Training Programmes, IMI16) deals with the education of pharmaceutical medicine (PhM).

These developments are only in their infancy in the emerging world, since there is only limited historic experience of university-based organisations in clinical research. India, for example, is characterised by large trial centres with thousands of patients, most of which are privately owned without a major academic background. China, however, due to a stronger central governance, has started significant efforts to establish accredited research sites under the umbrella of governmental and academic control and guidance. Apart from the special political situation of China, such a model is regarded as a useful tool for successful quality management in order to establish and guarantee the credibility of clinical trial centres. With a similar goal in mind, the US has successfully started the concept of rewards to academic centres. The National Institute of Health (NIH) has made translational research a priority, forming centres of translational research at its institutes and launching the Clinical and Translational Science Award (CTSA) programme in 2006. With 24 CTSA-funded academic centres already established, other universities are transforming themselves to compete for upcoming CTSA grants.
By 2012, the NIH expects to fund 60 such centres with a budget of $500 million per year. The hallmarks of such activities are training and education of research staff (5). Besides academic centres, foundations, industry, disease-related organisations, individual hospitals and health systems have also established translational research programmes, and at least two journals (Translational Medicine and the Journal of Translational Medicine) are devoted to the topic.

In the European environment, translational research, training and education have become central to the European Commission's €6 billion budget for health-related research, and the United Kingdom has invested £450 million over five years to establish translational research centres (5).

Such or similar activities are particularly useful to augment the credibility of data generated, and would be rewarded by the regulatory agencies. Both USFDA and EMEA have largely increased their auditing efforts for two major reasons: one is to detect fraud and misconduct of clinical research globally; the other one is to better understand whether data from emerging countries are compatible with Western standards in the context of medical science, ethical standards, etc. As a consequence, auditors are sent today to virtually all new emerging countries on a routine basis. The USFDA even opened its first office in Beijing in November 2008, and this will soon be followed by offices in India (6).

These activities have led to a larger focus on the role of Ethical Review Boards (ERBs), and ERB audits as performed in the US will also be more common in the future in emerging countries (1). Therefore adequate selection, training and education of ERB members in emerging markets will be essential in the future. The VSCR has for some years already been successfully running such training for ERB members in emerging countries, with a special focus on the African continent, which is struggling to cope on the quality front in their research efforts for diseases like AIDS, malaria and multi-resistant tuberculosis.

In conclusion, the large wave of clinical research in emerging countries has to be urgently paralleled by increased efforts in education and training. Providers of courses should preferably have an academic background or academic affiliation, and should be able to provide accreditation and CME credits. These efforts have to be spread to all participants involved in clinical research: academic centres, pharma and CRO personnel as well as ERB members. It needs adequate reflection when building the budgets and business plans of involved parties such as academic or non-academic trial sites, research personnel in both pharma and CROs, and for ERB members. Only thus can the process of globalisation of clinical research be followed through successfully and remain sustainable for the future. ■

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Vienna School of Clinical Research

BUILDING BRIDGES THROUGH TRAINING AND EDUCATION

The Vienna School of Clinical Research (VSCR) is an international non-profit organisation dedicated to continuing education of physicians and other experts who are involved in clinical research. The VSCR has trained more than 4000 experts from 90 countries over the last 8 years. Since 2001, approximately 20 different course modules have been developed, involving an international faculty of around 150 experts from more than 40 different countries. The courses cover topics relevant to clinical trialists including GCP, trial design and methodology, evidence based medicine, biostatistics, clinical epidemiology, ethics, publication, project management and health outcomes research.

This educational programme aims at optimising clinical research by minimising risks and cost while maximising the scientific value as well as ethical and quality standards. Based on a partnership between public bodies (City of Vienna, Austrian Government, European Commission), academic centres (15 universities in Europe, US and Africa) and the private sector (pharma and other industry), the VSCR promotes international dialogue and exchange, thus building bridges across stakeholders.

Vienna School of Clinical Research

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Role of the ICH-GCG (Global Cooperation Group) in facilitating the roll-out of ICH in non-ICH regions and countries

Introduction

Since ICH (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use) started in 1990, the global scheme of new drug development has drastically changed, especially in the last 10 years. Non-ICH regions are now an integral part of drug development, as the arena of clinical trials has expanded into non-ICH regions including Asia, Eastern Europe and other parts of the world. In addition, non-ICH countries are becoming major suppliers of active pharmaceutical ingredients (APIs) and drug products. ICH-GCG was established and expanded to meet this trend. In this article, the mission, framework, activities and evolution of ICH-GCG are described. In addition, implementation of ICH guidelines in non-ICH regions is discussed.

About ICH

In 1990, ICH was created among the three advanced regions for new drug development: the US, Europe and Japan. ICH consists of six parties (the regulator and industry from each of the three regions) and the observers (WHO, Health Canada and EFTA)(Fig 1).

Its objective was to improve the efficiency of new drug development and the registration process. By developing and implementing harmonised technical guidelines and standards, the ICH aimed to prevent duplication of clinical trials, minimise use of animal testing, and standardise the quality requirement without compromising the safety and effectiveness of drugs. Since 1990, ICH has generated more than 60 harmonised guidelines on technical requirements in safety, efficacy and quality. It also defined a common format for market application (i.e. Common Technical Document: CTD), an electronic format of CTD (eCTD), a medical dictionary (MedDRA), and other standards. Currently, there are 20 active topics which include new guideline topics and revision/maintenance of existing guidelines.

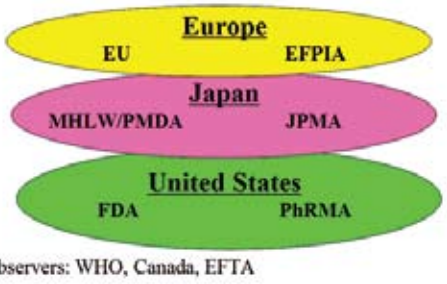

Fig1: The IHC World

These ICH activities provided scientifically sound means for quality, safety and efficacy of drugs, improved transparency, predictability and efficiency of regulatory process, and facilitated earlier availability of new therapies.

ICH-GCG

Mission and Framework: ICH initially focused on development of guidelines and standards for ICH regions. But soon there was a growing interest in ICH products beyond ICH regions in parallel with the growing trend for the non-ICH regions/countries to take part in the new drug development process. The Global Cooperation Group (GCG) was established in March 1999. Its name ("global" and "cooperation") indicates two-way collaboration, and reflects the desire to establish links between ICH and non-ICH regions. In the ICH structure, the GCG is positioned as a sub-committee under the Steering Committee. The GCG's initial mandate was to promote better understanding of ICH and its guidelines by information-sharing, including brochures which are posted to the ICH website, presentations by GCG members at international meetings, and responses to questions from non-ICH colleagues. The GCG was not created as a technical body but rather a facilitation body. Fig 2 lists the major evolutions of ICH-GCG, which are described below.

Invitation of Regional Harmonization Initiatives (RHIs)

Soon ICH found that a more proactive approach was necessary. In its Osaka meeting in 2003, the ICH decided to invite representatives from non-ICH regions to be part of the GCG membership. The expanded membership was called the Regional Harmonization Initiatives (RHIs). Criteria for being invited to join the RHI included (i) regions which are engaged in efforts to harmonise drug requirements across a defined group of countries, and (ii) regions which possess or develop mechanisms to disseminate information on GCG activities. Fig 3 shows the list of RHIs which have been invited to the ICH meetings since 2004.

Regulators Forum

The ICH also endorsed the Regulators Forum to discuss and share best practices among regulatory authorities on issues related to the implementation of ICH guidelines and impact on regulatory systems. The Regulators Forum complements the activities and objectives of GCG.

Year	Event
1990	ICH started
1999	GCG established
2004	Participation of Regional Harmonization Initiatives (RHIs)
2008	Participation of individual Drug Regulatory Agencies (DRAs)

Fig2: Evolution of ICH-GCG

Implementation of ICH guidelines in non-ICH regions

In the non-ICH regions/countries, there are (i) countries adopting ICH guidelines without changes, (ii) countries adapting ICH guidelines with some modifications, or (iii) countries not introducing the guidelines. But things are more complicated because there are countries implementing the guideline as it is, while there are countries implementing it in a different manner from what is written. So the issues are: (i) even if the guidelines look the same, sometimes actual implementation is different, (ii) on the other hand, even when there seems to be a big difference in guidelines, sometimes the actual implementation is very similar. The major problem for the industry is that even a slight difference in guidelines or implementation requires additional effort on the industry side, without any added value for the

APEC-LSIF
Asia-Pacific Economic Cooperation Life Science Innovation Forum

ASEAN-PPWG (Observer)
Association of the Southeast Asian Nations Pharmaceutical Product Working Group

GCC
Gulf Cooperation Council

PANDRH
Pan American Network for Drug Regulatory Harmonization

SADC
Southern African Development Community

Fig 3: List of Regional Harmonization Initiatives

The revised GCG mission statement adopted in the Brussels meeting in 2005 is given as: "To promote a mutual understanding of regional harmonization initiatives in order to facilitate the harmonization process related to ICH guidelines regionally and globally, and to facilitate the capacity of drug regulatory authorities and industry to utilize them". The RHIs brought in new opportunities, and the GCG which started with simple information-sharing, gradually shifted to implementation and training of ICH guidelines.

Invitation of individual Drug Regulatory Agencies (DRAs)

In the past two years, ICH has recognised a further need to meet current global drug development trends, where many non-ICH countries have joined the arena of clinical trials and manufacturing. The ICH concluded that certain individual countries can establish two-way collaboration / interaction with the ICH. Therefore, in the Yokohama meeting in October 2007, the ICH endorsed the idea to create an "Expanded GCG" by inviting a number of individual Drug Regulatory Agencies: i.e. (i) countries with advanced understanding of ICH concepts, (ii) countries which have been in the arena of multinational clinical trials, or (iii) countries functioning as global suppliers of APIs or drug products. Such participation would be distinct and complementary to the participation of RHI representatives. Individual countries/economies such as Australia, Brazil, China, Chinese Taipei, India, Korea, Russia, and Singapore were invited to ICH since the Portland meeting in June 2008. Fig 4 illustrates the geographical location of RHIs and DRAs.

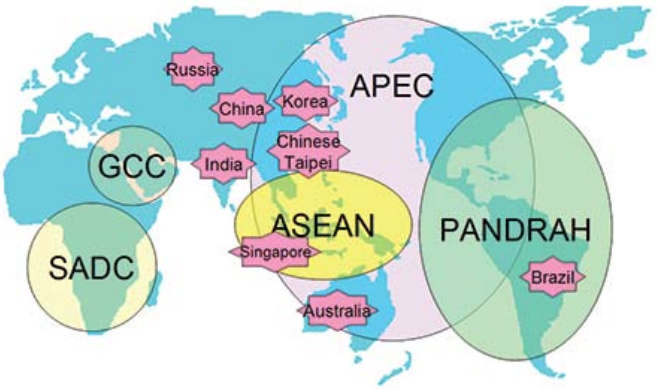

Fig 4: RHIs and DRAs

patients or public health. If there is a country requiring more than the ICH standard, there is a burden on the industry to accommodate the gap (Fig 5). Similarly, if there is a country requiring less than the ICH standard, there is a risk for the industry when we use the data globally, so there is a need to fill the gap to bring it up to the ICH standard anyway.

"Implementation" has a broad meaning and is difficult to define. Some of the implementation considerations would include e.g. proper understanding and interpretation of guidelines; proper translation of language and concepts; resource implications on regulators, industry and other parties; required skill sets, system and organisation; necessity for regulatory amendments; and impact on business processes. Any gap or difference will require additional efforts and thus may cause delay for the patients to access new drugs at the end.

Roles of RHIs/DRAs in implementation

For proper implementation, it is important for non-ICH countries to know the background information of the ICH guidelines, such as the concepts and thoughts behind the guideline and the rationale and process to build a guideline. Participation of RHIs and DRAs to ICH activities is very meaningful in this respect.

Fig 6 shows the RHIs and DRAs in the ICH scheme. The basic concept is to establish two-way dialogue and collaboration. The ICH can reach non-ICH regions much more easily and can better understand the needs of other regions and share practical issues. The non-ICH regions can better understand ICH guidelines and ICH process, and eventually spread the message for harmonisation. There are some specific measures for the non-ICH regions to understand ICH guidelines; (i) to participate in ICH meetings (e.g. GCG meetings, Regulators Forum, expert meetings), (ii) to have the chance to review Step 2 guidelines through webinars and mini-symposia, and (iii) to organise or participate in various training events.

Training - the key focus of GCG activities

So far, GCG has established various infrastructures including the framework and mechanism. These include the strategy document

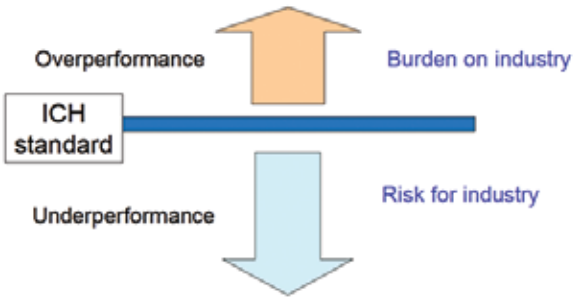

Fig 5: Slight difference requires additional efforts.

(basic policy), a procedural document for selection & prioritisation of training requests, a standard template for training requests, roles/responsibilities regarding organisation and coordination of training activities, a clearing house of training events and public access tools for information. Fig 7 shows the list of training events so far conducted or being planned. The list indicates two major areas of training, which are clinical studies and quality guidelines.

Potential development of GCG in the future

We anticipate more training events, more regional regulator/industry interaction and feedback, and earlier involvement of RHIs/DRAs in ICH activities. These will assure smoother implementation, and productive and transparent relationship between ICH and non-ICH regions. For the industry, the ideal situation is that ICH guidelines are adopted and implemented as written in many countries. The industry should play a major role in providing feedback to the regulators on actual implementation issues to facilitate the process.

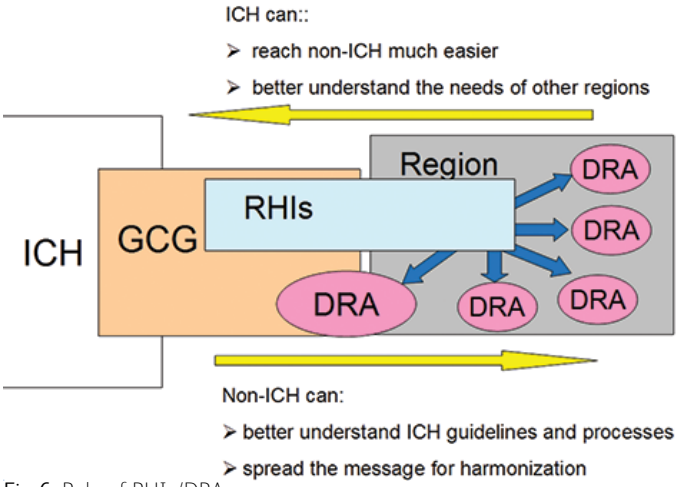

Fig 6: Role of RHIs/DRAs.

Important guiding principles of GCG

Fig 8 shows the important guiding principles of GCG. ICH does not get involved in regulatory requirements, but it only harmonises technical requirements. It does not define "what to do" but "how to do". It is up to each drug regulatory agency to define "what to do". However, we believe that ICH activities may also influence regulatory practice and sometimes lead to change in regulation if appropriate.

Mutual benefit is important: a Japanese industry perspective

The author strongly believes that collaboration between ICH and non-ICH regions must ensure benefit in both directions. For example, each country participating in a multinational clinical study must gain its own benefit. Sponsors in ICH regions conduct multinational studies to (i) increase speed of patient enrolment, thus achieving earlier launch of new drugs, (ii) decrease cost of development, or (iii) obtain clinical data from a different ethnic background. For non-ICH regions, one of the major benefits of participating in multinational clinical studies is to give the patients the opportunity for earlier access to new drugs. Until the ICH-GCP was introduced in non-ICH regions, development and registration were delayed many years from the ICH regions. Nowadays, multinational studies are resolving such drug lag in the non-ICH regions. In addition, the non-ICH regions can obtain efficacy and safety data in the population of interest, and the opportunity to participate in novel clinical research, thus bringing up the scientific standard in a global development setting. It is critical that all the players should be conscious of the benefit of others for complementary collaboration.

Date	Place	Title
Sep 2007	Korea	APEC Q8-10 Quality guideline Workshop (WS)
Mar 2008	Thailand	APEC preliminary WS on clinical trial assessment
May 2008	Thailand	APEC preliminary WS on clinical research inspections
Nov 08	Zambia	SADC Quality guideline WS
Dec 2008	China	APEC Quality guideline WS
Feb 2009	Thailand	APEC advanced WS on clinical trial assessment
Mar 2009	Thailand	APEC advanced WS on clinical research inspections
Nov 2009	Malaysia	ASEAN WS on MedDRA
Jan 2010	Malaysia	ASEAN WS on Q5C (Stability of biologics)
Mar 2010	Malaysia	ASEAN WS on Q8-10
early 2010	Saudi Arabia	GCC WS Quality guideline on biologics

Fig 7: Training opportunities.

➢ICH will not impose its views on any country or region – rather, to facilitate understanding and use of ICH

➢ The GCG will work with the WHO and other international organizations to achieve its goals

➢Recognition that some non-ICH countries may not be in a position to utilize ICH guidelines

Fig 8: Important Guiding Principles of GCG.

Conclusion

ICH is committed to responding to the needs of regions and countries interested in implementing ICH guidelines. The GCG is aiming at facilitation of global drug development through training, focusing on clinical studies and quality guidelines. Such mission, commitment and action plans were re-confirmed at the ICH meeting held in November 2009 in St. Louis, USA. Along with the worldwide expansion of the new drug development arena, the ICH-GCG is becoming a critical component of ICH activities.

We should be careful that these activities should not be one-way, from ICH to non-ICH. It is very important that both ICH and non-ICH regions respect each other and establish a win-win relationship, and eventually realise a truly harmonised drug development environment. The author strongly believes that as long as we keep the attitude to learn from each other and value mutual benefit, a constructive collaboration is always possible. ■

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SynCon International

Clinical Research Consultancy

Syncon International is a clinical research service provider in the Pharmaceutical Industry and Life Sciences. Syncon's services increase the cost-effectiveness of clinical trial budgets and decrease timelines. By partnering with strategic partners, Syncon provides customized integration of requisite core competencies to fulfil complex customer demands quickly and efficiently.
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The company is registered in the Netherlands Chamber of Commerce, and is based in the Netherlands, (Amsterdam) and Hungary (Budapest). Suzanne Pozsonyi, general manager is responsible for the everyday management of SynCon International, as well as coordinating services in the classical CEE countries. Services are supported by a network of strategic partners, with a global reach.
Part of the management group is Mr. Enrique Gaubeca, Managing Director, KLIXAR, - Latin America being an important part of the organization. Ms. Sue Hocker (US) is responsible for training and strategic communication, and Dr. Gabriella Gyovai, MD, ObGyn, (Hungary) provides overall medical advice.

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From 'Made in China' to 'Innovated in China'

Clinical Research Coming of Age

In his speech opening the Summer Davos meeting on 10 September of this year, Premier Wen Jiaboa stated that 'We will make China a country of innovation.' He specifically referred to bio-medicine as a key scientific and technological industry to be developed as 'a powerful engine of economic growth'.i These were not just hallowed words from the leader of 1.3 billion people: we are now beginning to see the specific efforts on the ground from key players in realising this national policy related to science, health, and economics. China is rapidly developing the infrastructure, industries, and regulatory frameworks needed to create a front-runner environment for not only clinical trials and pharmaceutical manufacturing, but also cutting edge innovation based on strong collaborations that include high levels of investment from private industry, mining of China's rich scientific and health professionals' communities, and the development of a political and regulatory environment to stimulate and reward novelty.

A significant backdrop to the push toward an innovative bio-medicine industry is the current round of high-level discussions on health reform in China, which include examining various approaches to health insurance and reimbursement schemes. In addition, on 1 October of this year the Third Amendment to the China Patent Law (first enacted in 1984) came into effect. This revised version of the law clearly promotes Chinese intellectual contributions and greater protection for investment in novel products in China. The new law also seeks to protect, while also promoting, the development of China's rich genetic resources and traditional knowledge. The Chinese government has taken steps with the patent law that not only reinforce its position on intellectual property protection within the international community, but also clearly promotes domestic investment in science and a Chinese pharma-biotech industry.

A significant example of the Chinese drive toward innovation is the Shanghai Clinical Research Center (SCRC), founded in 2008 by the Ministry of Science and Technology together with the Shanghai Municipality, that includes a total investment of 1 billion RMB

(approximately 150 million USD). SCRC's explicit mission is 'to be the vanguard for the globalization of clinical research in China', driving innovation and propelling the healthcare industry. In less than two years it has established a clinical research management centre with partnerships in eight major hospitals in Shanghai that delivers comprehensive Phase I through Phase III services. This includes a 56-bed hospital Phase I unit with Shanghai Xuhui Central Hospital. In addition SCRC has established a data management and statistics centre, a central lab, a biobank, a training centre (in collaboration with the Association for Clinical Research Professionals in the US), and an Independent Ethics Committee with distinguished Chinese leaders in ethics and science.

The push toward China as a centre for innovation is coming not only from within, but it is being reinforced from outside as well. This is highlighted by the recent announcement on 3 November by Novartis CEO Daniel Vasella explaining that the company will be investing 1.25 billion over the next five years to develop China as one of its top three global research bases. Significantly, the investment is largely focused on bringing Chinese scientific intelligence and creativity into a global strategy that targets both the fastest-growing healthcare market in the world, as well as building a new axis for global competitive drug development in the 21st century. While the Novartis announcement may well be to date the largest pharma research investment in China, more and more the major global companies are deepening and expanding their investments in the areas of both research and marketing in China. In the past two years Wyeth, GlaxoSmithKline, and AstraZeneca have all heavily invested in R&D spending in China.

The Chinese State Food and Drug Administration (SFDA) has taken important steps to build capacity for GCP inspections, collaborating with the US FDA and the EU EMEA on training and implementing an inspection programme. SFDA inspections focus not only on the review of specific clinical trials, but also on the certification of clinical trial sites. The aim is to improve the conduct and quality of clinical research at the sites. This year a draft Guideline for the Ethical Review of Clinical Trials at SFDA sites was released for comment, the third time since 2005 the SFDA has brought draft guidance for ethics committees forward for discussion. These guidelines are based strongly on the WHO Operational Guidelines for Ethics Committees That Review Biomedical Research (2000), but they also emphasise the important role ethical review plays in human subject protection, the need for ethics committees to work to international norms, and the need for quality management within ethics committees. SFDA inspections of certified clinical trial sites will now also include inspections of the ethics committees and their procedures. To this end the SFDA Training Center is also developing training programmes for members of ethics committees.

On 28 June this year the Chinese Clinical Trials Registry (ChiCTR) was officially launched at the West China Hospital, Sichuan University, in Chengdu, with international representation from the WHO and the GCPA. Developed in close cooperation with the WHO International Clinical Trial Registry Platform (ICTRP) and the international networks of Cochrane Groups, the registry is intended to further integrate clinical research in China into international standards. While China still needs to develop an official policy for the registration of clinical trials, and the publication of their results, ChiCTR provides a national framework integrated into the WHO's international efforts. The initiative also launched the Chinese Ethics Committee of Registering Clinical Trials (ChECRCT), in order to ensure an ethical dimension to the registration of clinical trials in the country.

While it is still well recognised within China, as well as outside the country, that there is a long road ahead for China to achieve a top place for drug innovation amongst the rapidly expanding global competition, clearly China is taking careful and measured steps which are bringing it steadily to the fore as a major player. The opening of three US FDA centres in China this year demonstrates the enormous relevance of the country to drug development. But China appears to be moving even more quickly and steadily from within toward remaking its image as a place of manufacturing to a place where innovation is becoming a hallmark for national and international industry, as well as economic growth and public health development. Increasingly the international leaders in drug innovation will have their attention turned to the developments in Chinese science and markets. ■

See http://news.xinhuanet.com/english/2009-09/11/content_12032065_2.htm (accessed: 12 November 2009)

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Conducting Studies on Devices in South Africa

South Africa offers a unique destination where high quality clinical data on devices can be obtained from highly skilled surgeons without the delays of getting regulatory approval to start the studies. This is because most devices are not regulated in South Africa, a country with a well established and highly regulated clinical trial industry with a global reputation of producing high quality clinical data.

The lack of governmental regulations controlling the well established device industry has led to the development of an informal system of self regulation and indirect regulation from the medical insurance companies. The regulation of device studies and practical issues encountered when conducting clinical trials on devices in South Africa are discussed below.

Regulation of commercial device use

Currently there is no regulatory body in South Africa with the legal authority to regulate all devices, so devices such as bandages, diagnostics, spinal implants or hip prostheses can be manufactured or imported into South Africa without any regulatory oversight. The only medical devices that are regulated are the devices that emit non-ionising radiation and those classified as high and medium risk electromedical devices. The level of regulation of these devices is minimal compared to the regulation of devices in the United States of America (USA) and within the European Union (EU), and the amount of information required to support a license application for these listed devices in South Africa is negligible compared to what is required by the USA Food and Drug Administration (FDA). The South African regulations, application forms and lists of regulated devices are available from the Directorate of Radiation Control [1].

The lack of regulatory oversight for medical devices is expected to change within the next two to five years as a new regulatory authority, the South African Health Products Regulatory Authority (SAHPRA), is currently being developed which will regulate all health products, cosmetics and foods. The Medicines and Related Substances Control Act, No. 101 of 1965, has been amended to provide the legal framework for the development of a parastatal organization that can function on behalf of the government but outside the bureaucratic infrastructure of government. The Medicines and Related Substances Amendment Act, No. 72 of 2008 [2] was assented to on 19 April 2009 but still needs to be enacted so there is still insufficient statutory power to implement the SAHRPA. The Act is expected to be enacted within the next national budget cycle once treasury has allocated the funds required to implement the regulatory authority. Therefore, it will still be several years until South Africa has completed the mammoth task of setting up a regulatory authority with the capacity to register the high number of devices currently available on the market. It is expected that once the first phases of the SAHPRA have been established the regulation of devices will be phased in by calling up high risk products first and over time increasing the scope of the regulatory authority to eventually encompass all medical devices.

"medical practitioners, especially practitioners in private practice, also need to protect their reputation among their patients so many practitioners will be hesitant to use a device that carries unknown or undue risk"

According to current legislation, the vast majority of devices are not regulated and can be used commercially irrespective of the level of risk associated with the device. The lack of formal regulation has led to the development of a multifaceted informal self regulation system. The facet of self regulation that probably has the most pronounced impact on the use of products locally is the acceptance of the devices by the various health practitioners who are generally well informed about global trends in device use. The communities of the various healthcare specialists are relatively small, so for implantable devices such as spinal devices for example, are implanted by a relatively small community of neurosurgeons or orthopaedic surgeons. If one of the leading surgeons has a good experience with the product, the chances are high that the device will be accepted by most surgeons, but the converse of this also applies as the products need to be accepted by the relatively close knit community where the surgeons closely guard their professional reputations and frequently discuss their experience with various products among themselves. The medical practitioners, especially practitioners in private practice, also need to protect their reputation among their patients so many practitioners will be hesitant to use a device that carries unknown or undue risk.

A second most influential mechanism of self regulation is the reimbursement of costly procedures required to implant most implantable devices. For example, hip replacement surgery is very expensive so the majority of hip replacements are paid for by either a medical insurance company (if the patient is treated in the private sector) or by the government (if the patient is treated in the public sector). The medical insurers and government procurement agencies

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are faced with the difficulty of deciding which devices should be reimbursed or not in an environment where the people with the decision making authority are often not trained to interpret safety and efficacy data on health products. The lack of reviewing competence within the insurance companies and procurement agencies has been compensated by the adoption of the general rule that if a device has a CE Mark or FDA approval, the medical insurers will fund the cost of the device and any expenses related to the use of the device. This does not mean that if a device has neither FDA approval nor a CE Mark that it will not be approved, it just means that the process for getting the product accepted by each insurer will probably be quicker if it has foreign approval. If a product is not marketed internationally, there is always the opportunity to provide supporting data, no matter how limited, to the decision makers within the insurance companies and procurement agencies to motivate the funding of the device.

Even though most devices used in South Africa are imported there are a couple of local companies that manufacture devices and diagnostics. Because of the relatively small size of the South African device market, the only way South African companies manufacturing cardiac stents, for example, can make a fair profit is to export devices to larger markets. So even though devices are not regulated locally, the regulation of devices internationally places indirect pressure on the local industry to increase the standards to comply with international manufacturing and clinical standards.

The enforcement of patent protections seems to be on an increase, and will more than likely increase the proportion of imported devices used locally which will add an additional pressure to self regulate the industry.

Regulation of clinical trials

In contrast to the lack of device regulation, the regulation of pharmaceutical products and clinical trials is well established. The medicines regulatory infrastructure has developed in conjunction with the development of an extensive regulatory and clinical trial industry in South Africa.

According to local regulations, all research on human subjects conducted in South Africa must comply with the Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa (SA GCP) [3] and must be conducted in accordance with the Declaration of Helsinki. The SA GCP guidelines are based on ICH E6, and are basically guidelines explaining how ICH should be applied in South Africa.

According to SA GCP, before any patients can be enrolled into a clinical trial, the trial needs to be approved by an ethics committee which is accredited by the National Health Research Ethics Committee (NHREC). The NHREC is a statutory body with several functions including the registration and auditing of ethics committees. A list of registered ethics committees is available on the NHREC website [4].

Clinical investigational sites all fall under either a private ethics committee or an institutional ethics committee, depending on whether the site is within a privately owned medical practice or whether it is affiliated to a public hospital. If patients are going to be treated in any of the public or government hospitals, including all academic institutions, the site will have to fall under the institutional ethics committee with jurisdiction over the specific hospital. A very convenient aspect of conducting studies in South Africa is that all privately owned sites nationwide can fall under one of the private ethics committees, such as Pharma-Ethics or SAMAREC. It is not unusual to have a trial with many private sites all falling under one ethics committee which makes the set-up of the study very cost effective and time efficient. A conventional South African practice that makes setting up studies even more efficient is that sponsors or contract research organisations (CROs) typically compile the ethics applications on behalf of investigators so because most ethics committees review an application within five weeks it can take as short as eight weeks from selecting the site to getting the site set-up and approved to enrol patients.

According to SA GCP and ISO 14155-1 it is essential that all trials are monitored by independent monitors throughout the study to ensure that all aspects of the study are conducted in accordance with all applicable regulations and guidelines.

Investigator requirements

According to MCC requirements, before a site can be approved as an investigational site:

- each site needs a principal investigator and at least one sub-investigator
- each investigator needs certification of GCP course attendance within the last three years and
- the principal investigator needs to have experience in at least two clinical trials.

Even though device studies do not fall under the jurisdiction of the MCC, most local ethics committees apply the MCC requirements to all clinical as these requirements increase the chances that investigators understand the fundamental differences between routine clinical care and investigational medicine and that the investigators are familiar with the operational and reporting challenges of clinical trials which in turns increases the probability that high quality data will be generated at all sites.

The potential benefits of increased data quality come at the cost of additional practical challenges as the availability of current GCP certification is often the rate limiting step in the set up of device studies especially when inexperienced or occasional investigators are selected to participate in the study. An additional challenge is that GCP certification is only accepted if the course was conducted by a recognised GCP course provider. The South African Clinical Research Association (SACRA)[5], under the auspices of the NHREC, is in the process of establishing standards for GCP courses. Within the next year, South African ethics committees and the MCC will only recognize GCP training from GCP course providers registered by the GCP evaluation committee. The content of all GCP courses will need to include the stipulated core material and will need to include required South African material which will exclude most GCP courses offered internationally.

The requirement for principal investigators to have experience in at least two previous clinical trials can also cause logistical challenges, but it is a requirement that is sometimes waived if the applicant can demonstrate that there is no possibility of getting an experienced principal investigator to oversee the trial at the specific site. Before setting up inexperienced sites, sponsors should consider that this requirement was implemented in response to previous problematic events which were attributed to the inexperience of the clinical research team, so for the benefit of the sponsor, it is highly recommended that inexperienced investigators are either given additional support from the sponsor or that the site is paired up with an experienced investigator who can mentor the investigator through the transition from routine clinical medicine to investigational medicine. The fundamental reason for the requirement is that GCP cannot be learnt from a textbook or taught within a short course and is best learnt on

the job when working under the guidance of an experienced trialist.

International regulations

The purpose of conducting clinical trials on devices in South Africa is very seldom limited to the collection of data to support local product commercialization, especially since there is no system for registering medical devices locally. Trials are typically conducted in South Africa to obtain data to support either an Investigational Device Exemption (IDE) or Premarket Approval (PMA) in the USA or to support a CE mark application in the EU. Therefore, the majority of device studies in South Africa are conducted in compliance with several international regulations.

Adverse event reporting

The main aspect of conducting studies according to the various guidelines that leads to confusion is the reporting of adverse events (AE), as the categorization of AEs differs between ISO 14155-1, 21 CFR Part 812 and SA GCP. The basic principles of reporting adverse events are the same in device and drug studies however the terminology is different and the definitions vary between the different device regulations or guidelines. In general, the safety reporting within device studies is often not adequate when compared to the standard of safety reporting in drug trials, and procedures implemented to reduce the workload of safety reporting have often been counterproductive and end up being less efficient than it would have been if forms and procedures used in drug studies were used.

The inconsistent definition of adverse events in the various guidelines makes it difficult to interchange safety data between datasets designed to meet the requirement in various regions after the study is complete. For example, the definitions in 21 CFR part 812 are limited to adverse events that are associated with the device so it is impossible to convert a safety dataset collected according to CRF requirements after trial is complete to a dataset that meets ISO requirements as ISO 14155-1 requires all associated and non-associated adverse events to be reported, but it is possible to convert adverse event data collected according to ISO definitions to meet CFR categories without obtaining any additional adverse event information. For this reason it is recommended that ISO 14155-1 classifications are used to report adverse events, which will provide flexibility to the data which will enable the data to be reported to any regulatory authority after the data has been cleaned and finalised.

The flow chart below shows a schematic representation of the timelines according to which adverse events should be reported in the various reports that are submitted to the ethics committees in South Africa. Since the trials are not regulated by any regulatory authority, the adverse event reports are only submitted to the ethics committee, and are prepared to be submitted to any foreign regulatory authority if needed. If reporting to regulatory authorities is needed, the timelines for reporting are very similar to the timelines included in the diagram.

Investigator grants

The negotiation of investigational grants is typically a lot faster in South Africa than in most other countries. One of the reasons for the process being so efficient is that it is very seldom that different amounts are negotiated with different investigators. The most typical practice for contract negotiation is for the sponsor to discuss an investigator fee with the lead investigator referred to as the national principal investigator, and once the NPI agrees that the value is acceptable the sponsor or CRO then presents the figures to all selected sites. Once all sites agree that the amount is acceptable the agreements are then prepared for each site. Once the final agreements are sent to the sites the agreements are typically signed as soon as the site coordinators are able to make the investigator sit down and sign the documents.

Because of the total lack of a system to register devices, "investigational devices" can be sold in South Africa, so it can become a little tricky when deciding who should pay for the procedures associated with the device. When researching relatively simple devices or diagnostics, the sponsor would be expected to cover all expenses specific to the study, however, the boundaries between what is covered by the sponsor and what is covered under the patients medical aid or own expenses becomes blurred for devices which require expensive procedures to implant the device. The decision of what portion of the total costs will be paid by the sponsor is usually dictated by the sponsor's internal policies. The full spectrum of approaches occurs, from the one extreme where the sponsor only provides the device and administrative costs associated with conducting a study where the patients or their medical insurers are expected to pay for all associated procedures and consumables, to the opposite extreme where the sponsors pay for all trial specific costs. There is no correct way to approach this issue as it is a multifaceted issue with several unapparent complexities. It is just recommended that the sponsor carefully considers all aspects of budgets including the amount of clinical data that can be obtained using internal budgets, the amount of additional work involved, the additional burden on the patients and the long term relationships with the investigators who will more than likely be the most prominent campaigners for the product once the product is commercialised.

Conclusion

Despite the lack of formal regulatory oversight of devices in South Africa, the device industry is largely ethical and well regulated through informal mechanisms of self regulation. The lack of formal regulation of devices superimposed on a country with a highly sophisticated medical system with highly skilled medical practitioners and a well established clinical trial industry currently provides a unique opportunity to collect quality clinical data that can be used to support regulatory submissions worldwide in a manner that is very efficient and cost effective. ■

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Chairperson of SACRA is the chairperson of the South African Clinical Research Association and an independent clinical trial manager. Lynn managed the South African office of Cato Research for the last 7 years where she managed clinical trials in several indications including spinal degeneration, acute stroke, multiple sclerosis, Crohn's disease, diabetes, hypertension and rare genetic disorders.

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TB Monitoring & Evaluation

An Q&A to look at how the challenge of Data Collection & Data Evaluation was overcome in this community based project

Dr. Patricia Lobo (Editorial Advisor of JCS) speaks with Dr. Dave Clark of Aurum Institute for Health Research on what clinical trials are being carried out into the prevention of TB.

1) What is the incidence/prevalence of TB in Africa today, particularly in South Africa?

South Africa is one of the 22 High Burden Countries that contribute approximately 80 % of the total global burden of all TB cases. South Africa has the seventh highest TB incidence in the world, and during the past decade the number of people with TB has increased threefold from 109/100,000 in 1996 to 341/100,000 in 2006. During this time the incidence has increased from 269 to 720 cases of TB per 100,000 population. In some areas, incidence exceeds 1300/100,000, and in the gold mining industry this number can double or even triple. In parallel, there has been an increase in the estimated prevalence of HIV in the adult population. At least 55 percent of TB patients in South Africa are infected with HIV. More than 5.4 million South Africans are HIV positive, and these individuals have a tenfold higher risk of developing TB than their HIV negative counterparts.

2) How is the WHO involved in trying to support S Africa to reduce the risk of TB, especially in people living with HIV?

The WHO has an office in South Africa and acts as a technical advisor on TB to the South African Department of Health. It also brings the resources of its Stop TB Department to stakeholders in the field of TB prevention, treatment, epidemiology, advocacy and monitoring and evaluation.

3) How has S Africa fared since 2004 and World TB Day (March 24th) when Mr Nelson Mandela called the world to action to do more to fight for TB?

Well, the country is not making sufficient progress to achieve the Millennium Development Goals in respect of TB. There is an urgent need to escalate the public health response to HIV and TB infection in South Africa, as discussed in "HIV infection and tuberculosis in South Africa: an urgent need to escalate the public health response" (Abdool Karim SS, Churchyard GJ et al., Lancet, Aug 2009).

4) How did the Aurum Institute come about and how is it funded?

The Aurum Institute for Health Research is an independent medical scientific organisation for the treatment of and research into epidemic and other diseases in developing countries. The negative impact of the poor understanding and management of these epidemics is vast, affecting individuals, communities and economies. The recognition of the huge advantages of controlling these diseases is Aurum's motivation.

Aurum has an international reputation for its work in the fields of tuberculosis and HIV/AIDS, and is the recipient of research and other grants from South African and international agencies and institutions for this work.

History

As most of our country's mineral deposits were in remote areas not serviced by state or private health services, the South African mining corporations set up their own medical services to care for the needs of their workforce. The service has been run by the various companies for the past 98 years.

Aurum Health Research (as it was then known) was established by AngloGold Ashanti in 1998 to gather together the large body of ad-hoc research, treatment knowledge and scientists working on or with the mines into an institution. It was tasked with conducting research into the surveillance, treatment and management of epidemic, occupational and other diseases occurring amongst mineworkers and their dependents. Aurum expanded its activities outside of mining industry needs, especially in response to international demand for quality treatment and research sites and programme development around HIV/AIDS- and tuberculosis-related projects.

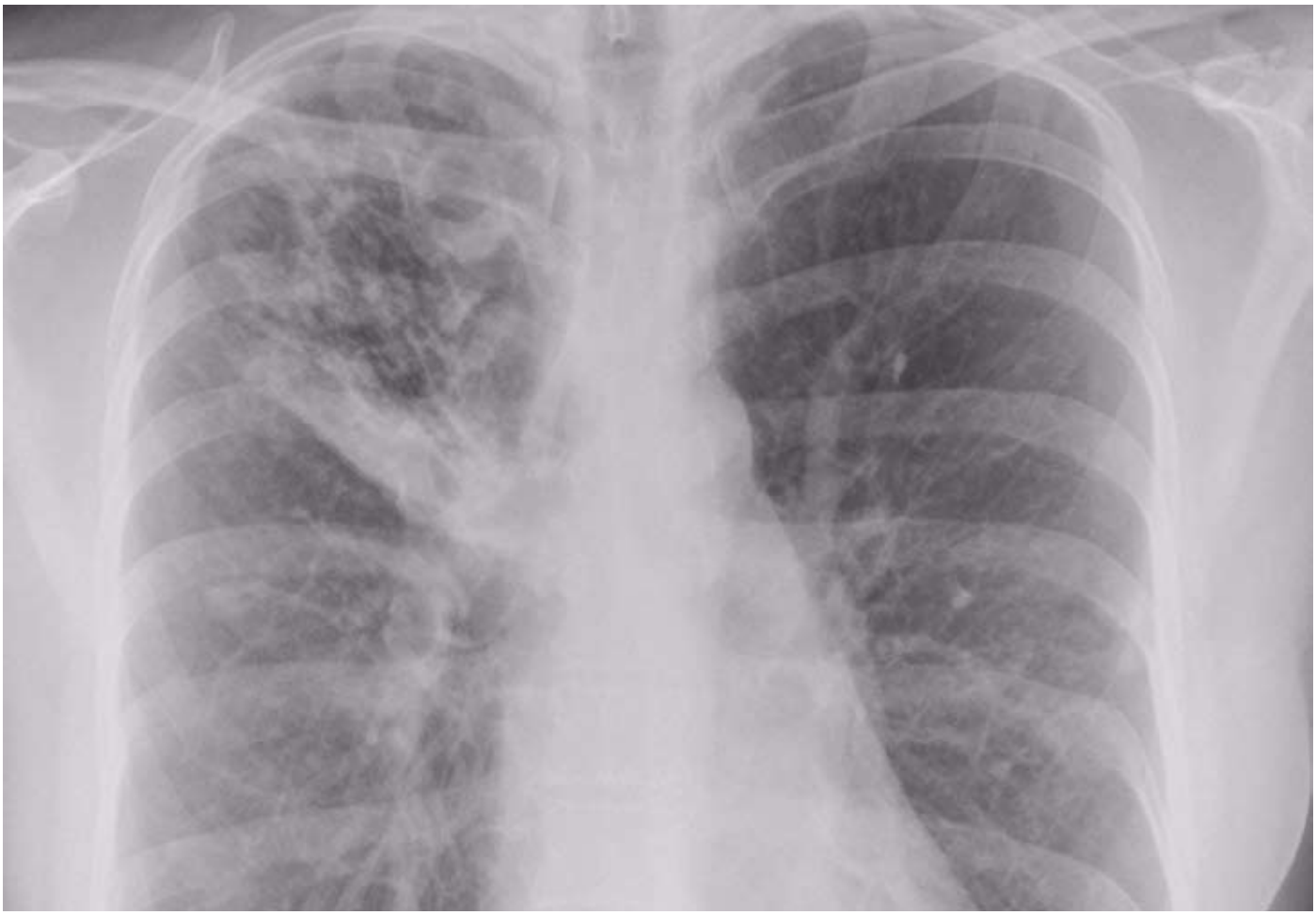
Aurum today

In 2005 The Aurum Institute was promulgated as an independent, not-for-profit Public Benefit Organisation. This positions the Aurum Institute to impartially represent the interests of working South Africans, their employers and the public. It has enjoyed significant success in informing, developing and working with communities within which its research work takes place.

Aurum is acknowledged by funders, companies, NGOs and communities as a partner capable of conducting ethical research and delivering reliable results. Aurum adds value by supplying the context, expertise and experience for our partners to make better-informed health-related management and treatment decisions.

5) What clinical trials are being carried out by Aurum into the prevention of TB, and is there data to show that the approaches are effective and safe?

We are carrying out a large preventive study into TB in the gold mining industry called Thibela TB. It is a cluster randomised public health study & Phase IV trial of isoniazid (INH) for community-wide preventive therapy of TB in gold miners, with about 70,000 participants in total (30,000 in the intervention arm). It must be noted that this is not a



vaccine study but a study into the preventive application of INH, one of the drugs used to treat TB. It is too early to publish any results as to the effectiveness of the strategy as the study is not yet complete. The safety data collected from nearly 30,000 participants thus far indicates that isoniazid is a safe drug for use in this indication of community-wide prevention of TB.

The Aurum Institute is involved in two TB vaccine studies which are in the early stages of site initialisation and development at present.

6) Are you conducting research into any new drug(s) to treat TB? Would you elaborate on any clinical trials ongoing or completed?

The first really new drug for TB in 40 years presently far enough along the development pipeline for efficacy trials, coded TMC207, is from Tibotec (more details can be obtained from www.Tibotec.com). There are, however, encouragingly a number of other new drugs in this pipeline, and the aim of global drug development bodies is to fast track these drugs into use as soon as safely and efficaciously possible. Aurum is involved in trial planning with Tibotec at present.
There are other studies into improving regimens in TB treatment in which Aurum is involved. One of these is called the Rifaquin study with St George's College, London, whilst another is called the Remox study. An internet search under these names will provide more detail, but both studies aim to use newer registered antimicrobials in addition to conventional TB treatment to shorten the duration of TB treatment from the present 6 months.

7) How is the data being collected from your TB prevention trials? What issues are you encountering in data capture?

The Thibela TB study is unique in that it is a paperless study using the Phase Forward InForm Unplugged Electronic Data Capture (EDC) system for all data management on the trial. This is a major undertaking for a public health study outside of the pharmaceutical industry, and is run at full GCP compliance. Challenges and triumphs over difficulty extend from data management planning, through issues of training and connectivity, to managing clinical images and ensuring data quality in this extremely large public health endeavour. Obviously cost control and study timeline management are ongoing issues in the study, but we know that this study would not have been feasible if we had attempted data management using a conventional paper-based approach. ■

David A. Clark, MBBCh, BCom, MBA *is the Deputy CEO of the Aurum Institute. Dave is strongly involved in the business services and strategic management of the company. His activities include the implementation of business and information technology solutions for financial, human resource and research data management to support the work of the scientific and clinical departments. He has a particular interest in systems design and implementation and the development of managerial leadership for NGO's and small companies. Dr. Clark qualified in medicine at Wits University in Johannesburg. He also holds a Masters degree in Business Administration and a Bachelor of Commerce Degree, as well as a Diploma in Health Services Management.*

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Biobanking for Our Future: Clinical Trials in Africa

On the 28th October 2009, BioAnalytical Research Corporation (BARC) South Africa launched a biobanking repository, the first of its kind on the African continent. This biobanking unit is a specialised repository facility designed to support clinical trial science research across Africa, and enable innovation in the management and treatment of diseases such as HIV/AIDS, tuberculosis and diabetes.

The long-term storage facility will help scientists crack diseases such as the HIV/AIDS codes as diagnostic tests, or with the aid and development of new biomarkers that may not have been discovered when the original development plans were written and the trials started. In these cases, stored samples maintained continually at the correct temperatures will be extremely beneficial during reanalysis and future research phases which offer an opportunity either in a scientific breakthrough towards disease treatment and improved management of the patient, or a time-saver by designing better prospective trials in the future.

This state-of-the-art facility, designed for the storage of clinical trial samples from across Africa, represents more than US$ 3 million in direct foreign investments into South Africa's health sector, with the Fred Hutchinson Cancer Research Centre (FHCRC), HIV Vaccine Trial Network (HVTN) and BARC working together to set up a first-class facility in South Africa.

"state-of-the-art facility, designed for the storage of clinical trial samples from across Africa, represents more than US$ 3 million in direct foreign investments into South Africa's health sector,"

The biobanking repository is destined to store more than 2 million clinical trial samples in -80oC ultra-low-temperature freezer storage, and 1 million samples in liquid nitrogen vapour phase (LN2). This will enable ongoing scientific testing in order to better understand disease codes - the repository provides ideal regulated and consistent storage conditions for samples to be stored in perpetuity, so that they are only retrieved for analysis when a test has been developed to use that sample to answer new questions.

This means that as science evolves and new forms of scientific testing are developed in new diagnostic assay techniques or biological markers, these new forms of analysis and testing of function can be applied to existing stored samples in order to advance knowledge and allow innovation in the management and treatment of disease. "If we want to be the generation that cracks the HIV/AIDS code, then this biobanking repository is the hub that will help this generation to do that" (Peter Meewes).

Dr. Julie McElrath, Co-Director of the Washington, DC-based HIV Vaccines Trials Network (HVTN), in discussing the launch, said "this extraordinary event is timely as the recent RV 144 Thai Trial results offer significant new hope for future success in HIV vaccine investigation. We anticipate that the HVTN South African clinical sites and BARC SA laboratories will lead the way."

Why is BARC Biobanking so special? Many labs have some basic capacity for sample storage – but this facility has taken into account all the industry compliance requirements for biobanking repositories, and has used the latest technology in order to ensure that the samples will be totally secure, and the viability and integrity of these samples will be maintained until such time as further analysis is required.

Cold chain management: what does 'viability of sample' mean to the running of the BARC unit? It means that total cold chain management standards and integrity of the sample is maintained throughout all business and storage processes within the BARC facility. This includes stringent monitoring of samples on arrival at the unit to assess the storage container and size used, as proper packaging is essential to maintaining sample integrity; the physical type of dry ice and quantities used which will all impact critically and may further compromise on fitness / viability of the samples prior to long-term storage. All processes are documented, ensuring a complete chain of custody from the time the samples arrive up to the time of shipment. Continual real-time temperature monitoring of samples held in storage will further ensure that no critical temperature threshold limits or violations are reached. This provides assurance in the knowledge that the best possible storage conditions available are maintained, upheld and controlled, giving reassurance that all samples are intact and fully viable on shipment and on arrival at the various research centres.

Viability means "capacity for survival". Viability of cells and tissues in experimental biology refers to the extent to which those cells and tissues are living: it has now been shown that the temperature at which frozen preparations are stored affects the length of time after which cells can be recovered. It is also recognised that the lower the storage temperature, the longer the viable storage period for the specified samples.

Different samples require different temperatures in order for optimal viability to be maintained – plasma and serum samples are best kept below -70oC, whereas the stability of frozen cells cannot be assured unless the material is maintained below -130°C as an

absolute maximum, with below -150°C being ideal. Consideration has to include that improper handling of material maintained at cryogenic temperatures can have a detrimental effect on the viability of frozen cells. The BARC Biobanking unit has been set up bearing in mind these critical temperature threshold limits, that have been mandated for viability. Every time a frozen vial is exposed to a warmer environment, however briefly, it experiences a change in temperature which can affect the viability of the sample, thus closing the window of opportunity available and impacting negatively on the scientific research and potential breakthrough.

A Center for HIV-AIDS Vaccine Immunology (CHAVI)CHAVI Study in 2007 showed that the maximum acceptable time for a cryovial taken from a liquid nitrogen transfer pan to be kept safely at room temperature (17.4°C) is 15 seconds1. The glass transitional phase (GTP) is a critical temperature point above which samples are impaired and thereafter rendered useless for further study. It is therefore imperative that samples maintained in BARC are kept well below the GTP.

Marta Bull, 2007, working at the HVTN, looked at parameters involved in blood collection, processing and shipping, and how they influence immunological function. Bull et al demonstrate that immunological function of cells that are cryo-preserved is affected critically by cryo-preservation procedures, and showed that cryo-preservation of Peripheral Blood Mononuclear Cells (PBMCs) must be processed and frozen within eight hours from the time of blood draw to maintain maximum function of the cells in immune-monitoring assays. These assays require PBMCs that have been isolated and cryo-preserved under strictly defined conditions to ensure optimal recovery, viability, and functionality2.

Bull describes three cold shipping methods that maintain immunological function in appropriately cryo-preserved PBMCs, and demonstrated that shipping PBMCs in LN2 showed slightly better results than shipment of PBMCs on dry ice. She also noted that shifting PBMCs to higher temperatures once they are stored in LN2 should be avoided at all costs, as immunological function would be impaired2.

Minus 80 oC freezer storage: water-cooled -80oC ultra-low-temperature freezers have been installed, allowing for direct heat exchange transfer from the condenser via the reticulation system to the cooling towers. This is the most efficient means of heat exchange mechanism available, and they also incorporate a number of backed-up operational systems to ensure continual operational functionality of all systems, including additional water supply and reservoirs. All operational and electrical systems are continually monitored in real time for mechanical and electrical functional of all the systems, including the backup system held in reserve. The water cooling system will result in a direct electrical consumption saving up to 40 % less electricity compared with other facilities of equal size.

This conservation of energy is critical for a biobanking unit of this capacity where the ambient temperature is already over 20oC for most of the year, and where heat extraction is critical for functionality of the freezers as well as for staff safety.

Carbon dioxide (CO2) cylinders are linked to each freezer and are continually monitored by real-time monitoring. Should the temperature be compromised due to power loss despite all the generators and substation power provision, these will maintain the temperatures required for up to 24 hours; samples can also be moved to a backup freezer that is always kept primed for the unlikely eventuality.

Liquid nitrogen cryo-storage: large, fully automated, microprocessor-controlled, archival liquid nitrogen refrigerators with the highest available level of sample security, with safe, efficient isothermal properties and dependable operational mechanisms available have been installed, with a holding capacity of 58,000 samples. Typical liquid nitrogen consumption of this refrigerator is less than nine litres per day, thus reducing wastage of LN2. In the vapour phase storage, temperatures throughout the archive refrigerator typically vary less than 8°C with dependable temperature stability at -187°C. Included is a vapour guard which guarantees that liquid can never come into

contact with any samples. All refrigerators are monitored continually with real-time monitoring. A primed backup liquid nitrogen refrigerator is available at all times should this be necessary.

BARC Biobanking is based in Johannesburg, the business hub of South Africa, and there are two different manufacturers of LN2 which ensures continuity of supply.

Sample handling: liquid nitrogen samples are all handled in temperature-monitored and regulated LN2 baths, ensuring that the glass transition phase (GTP) is not breached and that the quality of samples is maintained throughout their stay at BARC. Samples are shipped in cryo-shippers by IATA trained personnel. These shippers have a static holding time of 18 days and a field working time of 11 days.

All shipments are couriered by approved courier companies with expertise in cold chain logistics and management. Only standardised approved packaging containers and validated materials are used so as to ensure sample integrity throughout the cold chain process. Effective packing techniques protect samples during transit and allow for unexpected delays during shipment.

Risk assessments have been performed in all the critical areas, and the assessors are assured that the backup systems in place are more than adequate, and will cover the risk of any loss of power to any of the areas. Standard Operating Procedures for all areas are in place with fully trained and certified staff.

Safety:

Personnel training: the management team at BARC Biobanking unit has made the issue of safety of paramount importance, and has ensured that all staff are fully trained in the use of the safety equipment and in safety procedures before they are allowed to enter the environment. Staff members are also fully trained in the use of the required safety equipment to ensure personal safety at all levels.

Atmosphere monitoring & extraction systems: accredited systems are in place in order to assure constant monitoring of oxygen levels within the facility - this is so as to detect the slightest increase in the levels of the inert gas, nitrogen, as this is odourless, colourless and tasteless. Asphyxiation is an effect of this gas occurring in high levels, and could occur without any preliminary physiological sign that could alert the victim. Extraction and ventilation systems are continually operational throughout the facility, ensuring that acceptable oxygen levels are maintained within the facility - both CO2 and nitrogen gases are expelled continually, thereby affording staff and sponsors confidence in the safety of the environment3,4.

Cold chain monitoring systems: an FDA-approved system has been set up to ensure real-time continual monitoring of the temperature, equipment electronic systems, liquid detection monitors, acceptable oxygen levels and related equipment failures within the facility. All instrumentation monitoring is electronically documented, and any critical changes result in an SMS via two independent service providers to standby staff members.

Should the O2 levels fall below the acceptable limits, extraction fans are automatically activated to extract all the air within the freezer room facility, with an abundant supply of fresh air entering into the facility continually. Systems are all alarmed to ensure that any warnings of deviation out of the normal requirements will ensure an efficient return to normality within the shortest time period.

IT systems in BARC: the BARC Biobanking facility uses the Meditech LIMS system as well as the LDMS system for sample handling, management and shipping, and all LIMS systems are backed up offsite in order to ensure disaster management control.

This facility has been developed to allow South Africa to offer capacity for clinical trial samples to be retained in Africa, for use when developments arise. This future capacity is critical for us to ensure that we can grow capacity in both drug trial development and vaccine development, using African researchers to find solutions and cures for the ills of both the continent and the world.

"This future capacity is critical for us to ensure that we can grow capacity in both drug trial development and vaccine development, using African researchers to find solutions and cures for the ills of both the continent and the world."

Dr Nona Simelela, CEO of South African National Aids Committee (SANAC), opened the Unit for BARC. Her keynote address clearly outlined the realities of HIV/AIDS in our country, the need to move with urgency to attain the goal of an AIDS-free nation, and our role as clinical researchers in achieving it.

Together with our partners in research and development, BARC SA is committed to expediting the development of solutions in the management and treatment of HIV/AIDS and making a positive contribution towards the achievement of the 2011 targets.

Through this and other partnerships of like-minded individuals and organisations such as SANAC we hope to crack the HI virus in this generation. Therefore, we trust that this launch event also marked the beginning of a relationship with SANAC as we work together to define a new reality for Africa's disease burden and a legacy of good health for its people. ■

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D Jessica Trusler MB ChB (UCT), DCH (SA), DTM&H (Wits), FC(Path)CLIN (SA), MMED Clinical Pathology (Wits) *is the Medical Director of BARC SA. Jessica is a clinical pathologist who spent 5 years in Chemical Pathology and then moved to clinical trials laboratory management, and has been with BARC since May 2005.*

News

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PharmaVigilant demystifies clinical trial process costs and improves access to data by offering sponsors complete visibility

Total Visibility into Clinical Trial Process - Cuts Inefficiencies and Eliminates Unnecessary Spending

WESTBOROUGH, Mass., November 3, 2009 – Clinical research sponsors now have a faster, more cost- effective and comprehensive technology solution to manage their clinical trial data with PharmaVigilant, a clinical trial technology provider. PharmaVigilant is demystifying the clinical trial process by offering sponsors complete visibility and access into the collection and management of their clinical trial data, enabling them to isolate inefficiencies, achieve significant cost savings and increase time to market for their products.

Our solution was designed to give sponsors direct visibility into the process behind building their clinical study and delivering their trial data so that any inefficiencies and wasteful costs have no place to hide," said James DeSanti, Founder and Chief Executive Officer, PharmaVigilant. "Our hope is to disrupt the status quo of clinical trials and introduce a new way of doing things. Our cost-benefit to sponsors goes well beyond access to data – we cut the time on site by almost 50 percent with our remote monitoring solution, resulting in substantial savings, and by utilizing our suite of products we help sponsors significantly eliminate bottlenecks and delays at all levels. With PharmaVigilant I am excited to be in a unique position to bring to market a solution that can truly shift the way sponsors have traditionally approached their technology partnerships."

The Company offers a full suite of clinical trial technology offerings including Electronic Data Capture (EDC), data warehousing, Electronic Trial Master File System (eTMF), Form Development, Remote Source Document Verification (rSDV), study administration and an automated site payment system. PharmaVigilant focuses on Phase I-IV clinical trials, registries and other post-marketing studies. The technology has supported more than 200,000 patients in 14 countries across North America, Europe, Asia and Australia and continues to expand rapidly

For more information, visit www.pharmavigilant.com.

Parexel has established The Expert Office to provide a single point of contact for clients which want the CRO's team to assist them with optimising all aspects of the clinical trial process

The pharma industry is increasingly seeking to improve clinical trials in response to spiralling development times and costs, attrition of promising compounds and tightening budgets.

Given their focus on clinical trials contract research organisations (CRO) are at the forefront of this optimisation and Parexel believes its specialists, with expertise in regulations, business and science, can help companies.

To improve access to its experts Parexel has set up The Expert Office. This consists of specialists, many of whom are former regulators, pharma executives and leaders of medical institutes, who can tackle a range of issues which impact on clinical trials.

Parexel's team has experience in Phase I to IV and can help with study design.

Seventh Wave Laboratories will apply gastrointestinal modelling to the analysis of early stage drug candidates being developed by its customers.

The deal, unveiled at AAPS 2009 in Los Angeles, will see Dutch contract research organisation (CRO) TNO supply Seventh Wave with its TIM range of gastrointestinal models to help the latter's clients assess the behaviour of oral medications.

According to TNO the new contract offering, which will operate out of Seventh Wave's facility in Chesterfield, Missouri, will cut research timelines for preclinical drug development when it becomes operational in 2010.

Seventh Wave CEO John Sagartz said that: "With the TIM system available on site, we have another valuable tool to solve our customers' specific needs in formulation development and pharmakokinetics."

i3 partners with acurian to provide more robust site selection services to clinical trial sponsors

Pharmaceutical services company i3 announced today it has entered into an agreement with Acurian, a leading provider of patient recruitment and retention solutions, to provide study sponsors with a unique, more robust solution to recruit investigators for clinical trials. Acurian's vast patient database will be complemented by new i3 services that offer statistics for improved planning and identification of trial sites with greater access to appropriate patient populations.

With its proprietary access to a large database of information relating to private insurance claims, i3 can identify potential investigators throughout the United States and rank them according to the number of patients available who match the required study-specific criteria. The effectiveness of this informatics capability was confirmed in a study that i3 published earlier this year, which demonstrated that the top-ranking investigators enroll patients twice as fast. With 70 percent of all trials missing their timelines, according to an industry survey, the application of i3's clinical informatics can make an appreciable difference in meeting customers' enrollment goals.
Patients visit Acurian.com and affiliated sources to sign up voluntarily for information about upcoming clinical trials of interest. This direct-to-patient approach has netted Acurian a database of over 50 million patients who have self-reported a wide variety of ailments and want to receive healthcare information, including clinical trial opportunities in their local area.

"Pairing i3's clinical informatics solutions with Acurian's patient assets will offer a unique product to the marketplace and particularly benefit sponsors of studies anticipating or experiencing enrollment issues," said Tom Abbott, president of i3 Pharma Informatics. "It also represents an additional opportunity to increase i3's brand penetration among pharmaceutical, biotech, and medical device sponsors."
"This agreement will further cement our reputation as a clinical research organization on which sponsors rely to execute difficult trials," said Bill Gwinn, vice president of Clinical Informatics at i3 Pharma Informatics. "78,000 investigators in i3's US database, combined with more than 50 million patients in Acurian's database, will yield a comprehensive view of sites, investigators, and patients to help our customers achieve their enrollment targets."

For more information, visit www.i3global.com.

Brecon strengthens board line-up

Brecon Pharmaceuticals, the leading supplier of commercial packaging and clinical trials supplies services for the pharmaceutical and healthcare sectors, has announced the appointment of Peter Belden as managing director.
Mr Belden previously held the post of senior vice-president, sales and marketing at Brecon's AmerisourceBergen Packaging Group sister company Anderson Packaging (Rockford, IL). He worked at Anderson for seven years and has extensive experience in the pharmaceutical packaging industry. A graduate of the University of Virginia, Mr Belden also has an MBA from DePaul University.
"Changing business models in the pharmaceutical industry mean that manufacturers are increasingly looking for full service packaging rather than ad hoc contract packaging. Brecon has made substantial investment in equipment and services to support pharmaceutical products through their entire life cycle, from early phase clinical trials to commercialisation and beyond, such that the company is perfectly positioned to offer exactly what the industry needs. And the ongoing harmonisation of capabilities at AmerisourceBergen Packaging Group companies enables us to extend our reach globally," affirms Mr Belden.

Simultaneous with Mr Belden's appointment, Andrew Billington has been promoted to senior director, operations. Mr Billington, who has been with Brecon for 17 years, is currently taking responsibility for the company's Lean Six Sigma and Operational Excellence initiatives.
"When it comes to getting a new chemical entity to market, every day counts," says Peter Belden. "No-one understands this better than the team at Brecon and it's this deep appreciation of the market we serve that will ensure we go on to achieve even greater success in the future."

China Sky One Medical, Inc.

("China Sky One Medical" or "the Company") (Nasdaq: CSKI), a leading fully integrated pharmaceutical company producing over-the-counter drugs in the People's Republic of China ("PRC"), announced that it obtained approvals from the State Food and Drug Administration (SFDA) in China for the production of Geranium ointment and Musk liniment for pain relief.
Geranium ointment is used to cure chronic eczema, carbuncle, furuncle and small scalds. Musk liniment is used to relieve the pain from scathe, wound, rheumatism and arthrosis. It can be used to treat skin sores and blood clots. There are only one or two competitors supplying these products to the market. Management expects that the two new products will have a large market potential since many patients in China are suffering from these diseases, especially in rural areas. The Company estimates that the two products combined will contribute $0.8 million to revenues in 2009 and potentially much more in 2010.
Source: China Sky One Medical, Inc

No clinical trials for SA healers

South Africa's outspoken health minister has said medicines used by traditional healers should not be subject to clinical trials.. Manto Tshabalala-Msimang warned against using what she called Western protocols for research and development. Medicines used for thousands of years should not become "bogged down in clinical trials", she said.
She was speaking during a meeting with traditional healers to discuss a draft policy to regulate the practice.
"We cannot use Western models of protocols for research and development," said the minister, although she added that she was not against clinical trials per se. The healers complain that the South African government has been too slow in implementing a law passed in 2005 aimed at integrating traditional medicine into the mainstream health system. Ms Tshabalala-Msimang has faced criticism in the past for suggesting garlic and vegetables be used to combat the spread of HIV.

World Courier has opened investigational drug storage facilities in South Africa and Australia, a move it says is in response to growth in the regions' clinical trials markets.

The rapid globalisation of the clinical trials market has created a need for infrastructure around the world and World Courier has responded, opening 11 drug storage depots.
World Courier's operations now includes sites in Johannesburg, South Africa and Melbourne, Australia. Asia, Latin America and Central and Eastern Europe (CEE) frequently dominate discussions about clinical trial globalisation but World Courier believes there are growth opportunities outside these regions.
Wayne Heyland, President and CEO of World Courier, claims that Africa and Australia "undertake over 15 per cent of current global clinical trials conducted outside North America, representing an annual estimated market of almost US $3bn (€2bn)".
Africa in particular represents a massive, treatment naive patient pool and contract research organisations (CRO) have begun to make moves into the continent.

Rwanda - A group of researchers announced the launch of a maiden clinical trial of a vaccine against malaria, which will benefit seven African countries, an authorised source in the Rwandan capital told JCS here.

The researchers met in Nairobi, Kenya, during the fifth multilateral forum on the initiative of the vaccine against malaria.
According to a statement, released by the African Initiative of the Fight Against Malaria (PATH-MVI), the new vaccine will be administered to some 16,000 people in Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique and Tanzania.
The trial is expected to assess the potential safety, tolerance and effectiveness of the product, GlaxoSmithKline Biologicals (GSK Bio).
"The new vaccine will help save thousands of human lives in Africa, where about 800,000 people die from malaria," said Dr. Patricia Njugunya, researcher at the KEMRI Centre, specialised in the design of vaccines against tropical diseases, especially malaria.
People to be vaccinated, who are between 6 to 17 years of age, will undergo a six month-treatment period, then a monitoring period of the safety and effectiveness of six months, according to the statement.
"This marks a crucial period in the fight against malaria after 10 years of research on malaria vaccine," said Dr. Joe Cohen, initiator of the vaccine.
Malaria is the leading cause of infant mortality in Africa.
In Rwanda, official statistics show that 62 infants among the 1,000 live births die each year from malaria before reaching age five.

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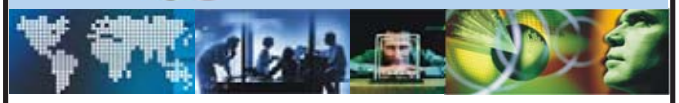

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