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JOURNAL FOR CLINICAL STUDIES

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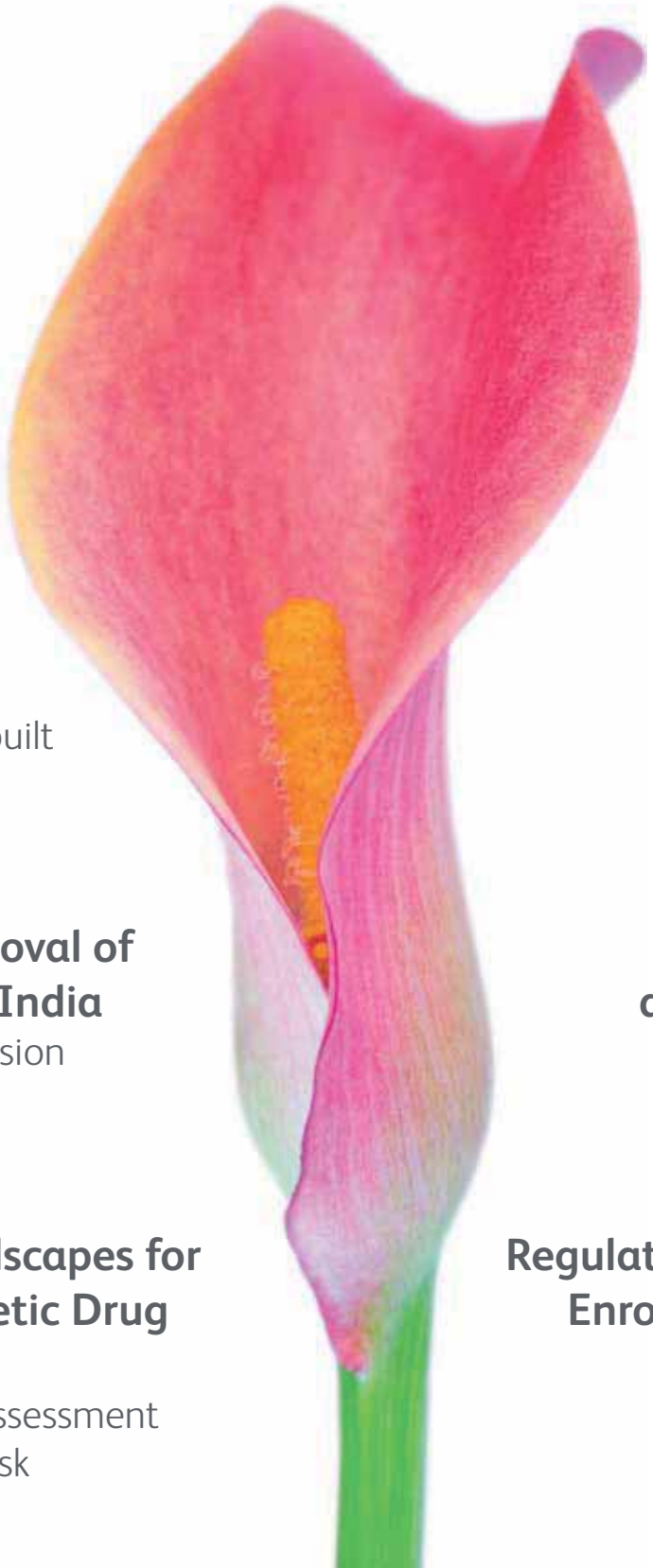

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Regulatory Timelines and Enrolment Potential in South Africa
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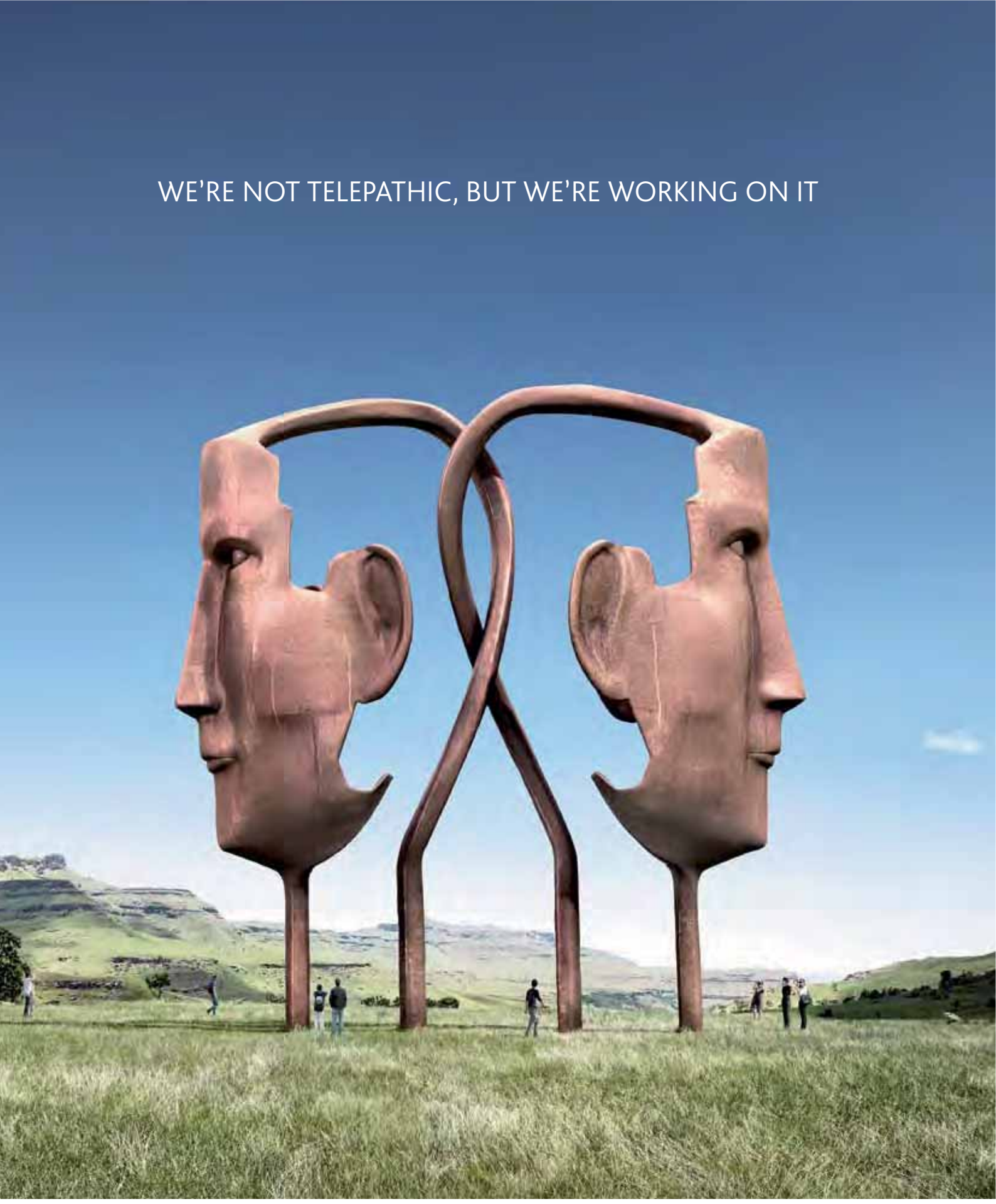

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Contents

Contents

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Editorial Advisory Keynote

A happy New Year to you! As our first issue of JCS 2010 goes out to you readers, we hear that the UK economy has come out of recession, after figures showed it had grown. The UK's had been the last major economy still in recession, as Germany, France, Japan and the US emerged from recession last year. According to official data from the Office of National Statistics (ONS), the UK economy grew by just 0.1% in the last three months of 2009, compared to the previous quarter. During the 18 months of recession, public borrowing increased to an estimated £178bn, while output slumped by 6%. Some commentators are less jubilant on the ONS figures as they recognise that there's more than a good chance that the 0.1% growth in Q4 will end up being revised downwards. Would it be tempting to predict a positive outlook for the life science industry for 2010? Reductions in health spending and industry job cuts could have an impact on the market, but an ageing population and a health service under pressure will guarantee an increasing demand for pharmaceuticals. According to Epsicon (The Pharmaceutical Market – January 2010), the UK pharmaceutical market is set to experience moderate growth over the coming years, tempered slightly by the effects of the economic recession. Public spending cuts are likely, as public debt continues to increase, and health expenditure is set to suffer as a result.

I was particularly impressed by the 8th Annual Partnerships in Clinical Trials Congress and Exhibition by Informa, held in early November 2009 in Rotterdam. The meeting is an annual review of the industry's best practice clinical partnerships between sponsors, CROs and other service providers. The conference Chair, John Sergeant, investigated the topic of how much the recession has impacted on clinical partnerships. Anatole Kaletsky, Associate Editor and Principal Economic Commentator of The Times, presented with great clarity an examination of the economic downturn and its impact on the pharmaceutical industry. The case study presented by Eli Lilly and Covance about risk-sharing in a successful clinical partnership was very well received. Jeffrey P. McMullen, President and Chief Executive Officer, PharmaNet Development Group, Inc., gave a detailed analysis of CRO growth opportunities in a more challenging market environment.

One of the major challenges facing globalisation of clinical trials is the recruitment of patients into clinical trials. As the demand for larger patient pools grows, countries with less experience are quickly emerging as clinical trial sites. The most prominent emerging regions include CEE, Latin America, and Asia. This globalisation trend is introducing new challenges in conducting clinical research, including language and cultural barriers. These create significant barriers to patient recruitment, especially in obtaining informed consent. In addition, regulatory approval processes and timelines in each country vary considerably. Lynn Katsoulis discusses improvements in the regulatory standards, timelines and enrolment potential in South Africa, whilst Rajam Jaishankar reviews the latest from the DCGI (Drugs Controller General India) (see pages 12 and 14 respectively) and Ryan Simper looks at the demand for language services providers in the changing clinical development world (page 52). On the patient recruitment front, my colleague Keith Thrower assesses the benefits and problems in emerging markets (page 38), whilst Oscar Podesta and Matthew McLoughlin focus on clinical research in Latin America (pages 16 and 27 respectively), Anna Ravdel on Russia (page 24), Rabinder Buttar on Diabetes in India & the Gulf Region (page 42) and Rayna Shahrouri on Tunisia (page 18).

I am looking forward to meeting visitors to the forthcoming meetings listed on our events page, where you can pick up a copy of Journal for Clinical Studies hot off the press for hours of interesting reading. Thank you for your support, and keep the articles rolling in.

Dr Patricia Lobo, Life Science Business Solutions

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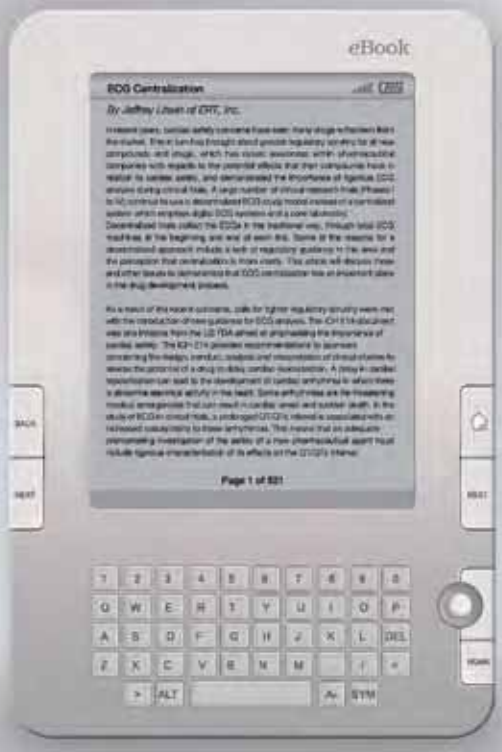

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FDA Debarment and Disqualification Efforts

Published in September 2009, the US Government Accountability Office (GAO) Report, Oversight of Clinical Investigators: Action Needed to Improve Timeliness and Enhance Scope of FDA's Debarment and Disqualification Processes for Medical Product Investigators, examined the US Food and Drug Administration's (FDA's) debarment and disqualification processes.(1) The GAO examined the length of time the debarment and disqualification processes had taken and factors for those timeframes.

The GAO reviewed laws, regulations, and FDA files through November 5, 2008, for all investigators, study coordinators and sub-investigators for whom the FDA pursued debarment since receiving debarment authority in 1992, and all clinical investigators for whom the FDA pursued disqualification since adopting its current process for initiating proceedings in 1998.

Under current law, the FDA can ban, or debar, individuals known to have broken the law from working for companies with approved or pending drug applications at the FDA. The agency can also disqualify researchers conducting clinical testing of new drugs and devices, when the FDA determines that they have not followed the rules intended to protect study subjects. The FDA can also disqualify a clinical investigator for manipulation of data (inaccurately reporting study findings).

The GAO study found that completed proceedings during the study period took from just over three months to more than ten years, with a median of 2.8 years. The GAO cited FDA inefficiencies — internal control weaknesses and competing priorities — as factors contributing to the delays. The GAO report includes three recommendations for action. The first urges the FDA to pursue debarment authority for medical devices consistent with procedures for drugs and biologics. Under current law, an individual may have been debarred from involvement with drugs and biologics, but may not necessarily be precluded from involvement with other FDA-regulated products, such as medical devices.

The second GAO recommendation is to amend regulations to disqualify an investigator who was found to have engaged in misconduct from any clinical investigation. The third recommendation made by the GAO was that the FDA take the necessary steps to monitor compliance with recently established timeframes for debarment and disqualification proceedings, and take appropriate action when those are not met. In August 2008, prior to the release of the GAO report, the FDA put forth efforts to prevent non-compliant investigators and others from participating in new product development.(2) The revamped debarment and disqualification procedures, which include increased staffing and centralised coordination, ensure that more rapid, transparent, and consistent actions are taken.(3)

The FDA's Center for Drug Evaluation and Research (CDER) had begun making changes and setting priorities in 2008, including a July 2009 change in organisational structure of the Office of Compliance, Division of Scientific Investigations (DSI), an office that focuses predominantly on serious allegations of non-compliance, and cases that appear to warrant disqualification. Since implementing changes to DSI's structure and making improvements to the disqualification process, the FDA timeframes under the new procedures for debarment have resulted in debarment within a year of the individual's or company's conviction.(4) CDER reports improvement in the disqualification process, indicating 0.5 years for procedures between 2006 and 2008, and 4.6 months in fiscal year 2008. ■

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1 GAO Report: Oversight of Clinical Investigators: Action Needed to Improve Timeliness and Enhance Scope of FDA's Debarment and Disqualification Processes for Medical Product Investigators (GAO-09-807), 25-Sep-2009. Available at: http://www.gao.gov/products/GAO-09-807

2 Food and Drug Administration Press Release: FDA Enhances Speed and Transparency of Actions Taken Against Misconduct in Drug and Device Development, 07-Aug-2009. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm176040.htm

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4 Food and Drug Administration Page: The Role of FDA's Center for Drug Evaluation and Research (CDER) in Disqualifying Researchers from Clinical Trials for New Medications. Accessed 2-Nov-2009. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ConductingClinicalTrials/ucm188693.htm

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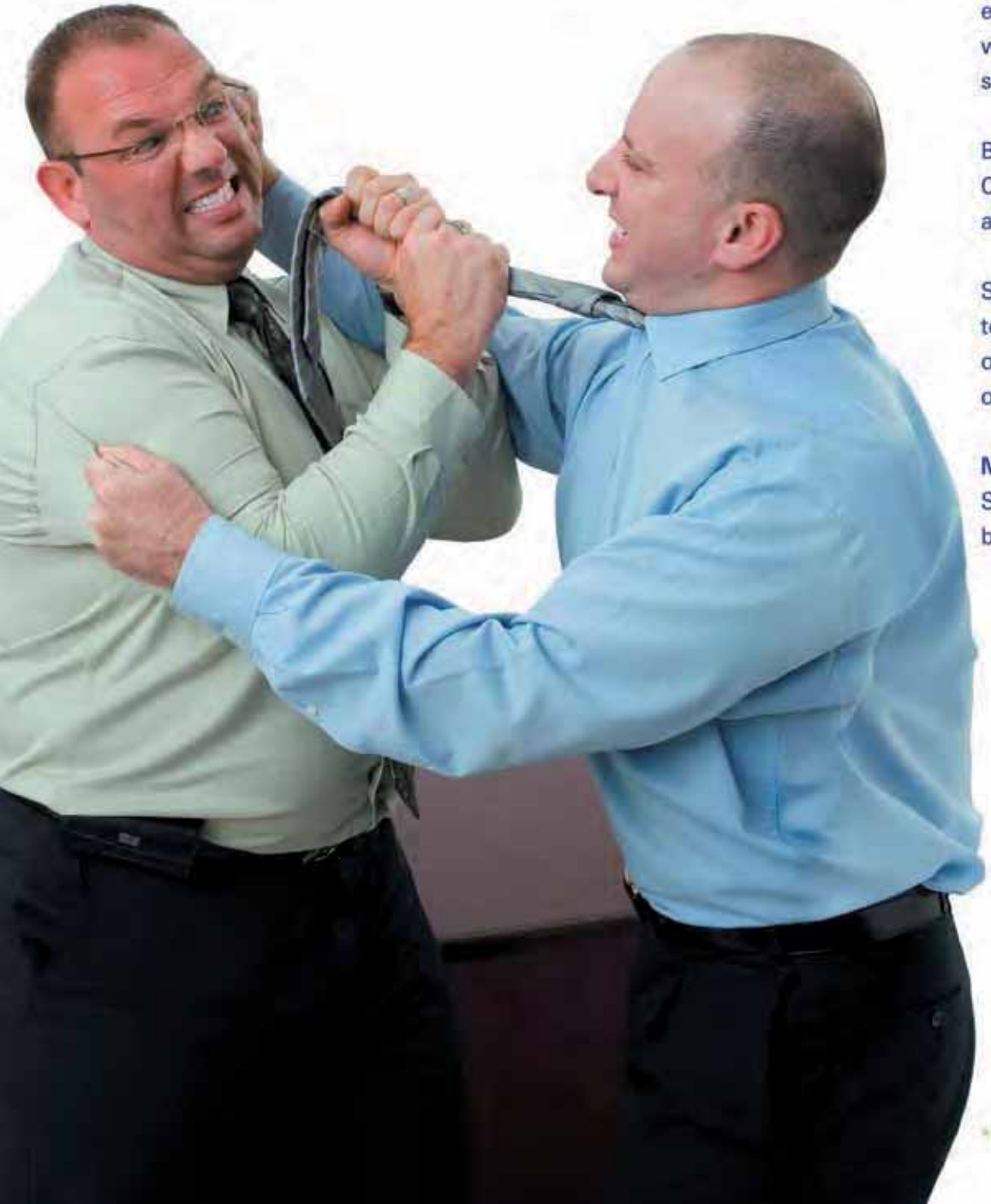

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Regulatory Timelines and Enrolment Potential in South Africa Starting to Improve

South Africa has been a role player in the clinical trial industry since the 1960s, and over the years has developed a well-earned reputation as a destination which for several indication provides high quality data and one of the highest enrolment rates per site per month. Unfortunately over the last decade many companies have experienced unacceptably long delays in obtaining regulatory approval for clinical trials, which has tarnished the country's reputation for conducting studies. However, slow regulatory approvals will soon be an issue of the past, which will liberate South Africa to meet its potential as an excellent destination for clinical trials.

South Africa – still offering high quality data and high recruitment rates

The high recruitment rates obtained in South Africa have often been obscured by the choice of the clinical trial metric used to measure overall enrolment, which captures the overall enrolment rate rather than using a normalised metric to show recruitment rates per site over a standard unit of time during which the sites were able to enrol patients. The total enrolment per trial per country is not a good indicator of enrolment potential unless the enrolment period is normalised for all countries. The problem with many trials conducted in South Africa is that the enrolment periods were reduced because initiation was delayed by two compounding factors: 1) South Africa was included as a rescue country once enrolment fell behind target, and 2) regulatory approval was delayed.

A metric which is not often measured is the time between selection of a country and initiation of 90 % or 100 % of all sites, which is a more meaningful measure of performance in a country. For this metric, even with delayed regulatory approvals, South Africa is one of the highest-performing countries. Regulatory approval is the main rate-limiting step in starting up studies in South Africa. Contract negotiations, issuance of import licenses, ethics committee approvals or translations very seldom delay the start-up of a study. This means that once Medicine Control Council (MCC) approval is obtained all sites can be initiated. Efficient clinical trial management teams utilise the time taken to obtain regulatory approval to complete all preparation for a study, so as soon as the MCC approval letter is obtained, all sites can be initiated within about two weeks if activities are well planned.

Metrics in the internal databases of several companies conducting multinational clinical trials show that despite the delayed start-up of studies in South Africa, a higher proportion of sites than in other countries enrol patients, and unusually high proportions of sites meet initial recruitment targets, provided the recruitment time was not unrealistically short, and for many studies the highest-recruiting sites globally have been South African sites, particularly in conditions which are prevalent in South Africa such as hypertension, stroke, diabetes and HIV.

Upcoming improvements in regulatory turnaround times

Historically, regulatory approval times in South Africa were short, often less than two months, but average regulatory approval times started to increase during the late 1990s, when the level of review increased and administrative expertise in the MRA were lost. The mean time taken to approve a clinical trial application increased until it reached a peak of about 6.8 months in 2008.

The reason for the increased regulatory approval times was mainly as a result of political changes in South Africa, as a liberation party that did not have the experience or expertise to run large administrative departments came into power. A problem experienced many times around the world. The African National Congress (ANC), the first fully democratically elected government, has been in power since 1994 with the third elected president currently in office, and is now having to deal with the consequences of over a decade of poor governance in many areas of government, including the regulation of medicines. Thankfully, since the current administration took office under the leadership of President Jacob Zuma in May 2009 many dramatic changes have been implemented with encouraging improvements which are starting to become apparent in the improved regulatory review timelines. Unlike before, the current minister of health, Dr Aaron Motsoaledi, openly acknowledges the numerous problems within the health sector and is tackling many challenges by recruiting competent individuals who have the expertise, experience and initiative to repair some of the damage caused over the last decade.

Most of the improvements to date have been a result of improved management, but even more improvements are expected as the Medicines Regulatory Authority (MRA) is in the process of being completely overhauled, as the current system of reviewing clinical trial applications (CTA) and medicine marketing applications is antiquated and inadequate. The current system relies on external reviewers (previously they were predominantly academics with minimal involvement in clinical trials) to review applications for a nominal financial reward, and then present their recommendations to fellow members of the Clinical Trial Committee (CTC). The CTC's recommendations are then presented to the MCC, which usually meets about six weeks after the CTC meeting. The main problems with the system are the two-tiered review with time delays between each committee meeting, the inefficient reviews by the independent reviewers, and poor administrative management. Previously the MRA did not enter into service level agreements with the independent reviewers, which meant that there were no prescribed timelines for reviews and the MRA had no way of holding the reviewers accountable for missing meetings or taking too long to review applications. The consequence was that many applications sat on reviewers' desks for several months, which translated into delayed approvals and shortened recruitment periods. Recently the administration of the review process has become far more efficient, reviewers have signed

service level agreements, and several academics who have experience in conducting clinical trials have been elected as reviewers onto the CTC. All these factors have improved the overall motivation of the CTC and MRA to meet the tight timelines inherent in clinical trials. There is no longer a backlog of clinical trial applications, and all applications are now being reviewed within the review cycle into which they are submitted, and a high proportion of initial applications are now being approved within the targeted three-month review period. However, the MRA is still working on clearing the backlog of applications to amend protocols and investigators working on a study, which should be cleared within the next few months.

Further improvements and reductions in timelines are expected once the new regulatory authority has been formed and new systems have been implemented to review and approve applications, but it is going to take time to rebuild a regulatory authority with sufficient manpower and experience to meet the high expectations of the South African Clinical Research Industry. Once South African sites are given longer periods to enrol patients, the overall country will once again become one of the choice destinations for studies, provided that the country can maintain its cost competitiveness, and that the capacity to conduct studies increases proportionally to the increased number of studies approved in the country.

SACRA

One of the positive outcomes of the challenges caused by having an inefficient regulatory authority regulating an efficient and well-developed industry has been the formation of a coherent industry association, the South African Clinical Research Association (SACRA), which enabled the industry to efficiently collect and share information about unexpected changes. SACRA is a dynamic and very active national association representing all aspects of the clinical trial industry. It provides a platform for networking and sharing of information relevant to conducting clinical trials within South Africa. Involvement in SACRA activities enables members of the organisation to remain abreast of local and global developments relevant to South Africa through quarterly meetings in Johannesburg and Cape Town, an annual conference typically held during the third quarter of each year, and a website (www.sacra.za.net). Membership of SACRA is open to all individuals directly involved in clinical research irrespective of their location. The association is managed by an executive committee made up of eight to ten volunteers who are elected annually to represent the various disciplines within the clinical research industry. The executive committee is made up of clinical research associates, investigators, site coordinators, laboratory technicians and couriers, who work for pharmaceutical companies, clinical research organisations, laboratories, site management organisations, investigational sites and as independent consultants to ensure that all aspects of industry are fully represented. ■

Lynn Katsoulis PhD, Independent Consultant 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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Regulatory Approval of Clinical Trials - DCGI with a New Vision

India's equivalent to the US Food and Drug Administration (FDA) and European Medicines Agency (EMEA) is the office of the Drugs Controller General (India) (t). The DCGI is the official federal agency responsible for all pharmaceutical-related issues in India described in the Drug and Cosmetics Rules, 2005 (DCR). Clinical trials are regulated per Schedule Y of the DCR.

This decade has given the pharmaceutical industry a new perspective. Notable among these is the phenomenal growth of the Contract Research Organization (CRO) industry and the emergence of India as an important clinical research destination in the world. This has made international sponsors expect more from the regulatory body. Additionally, the growth of pharmaceutical companies has resulted in an exceptional increase in exports to regulated markets across the globe. However the regulatory system has not kept pace with the growth of the industry.

The Indian regulatory system is becoming transparent, informing people of benefits as well as risks, and has ended up being right. Under the right leadership, even the conservative government organisations such as the Drugs Controller General of India can take informed risks and make a huge difference. The DCGI has taken many steps in the recent past that have set good examples for the industry. Registration of CROs with the DCGI allows them to know who is doing what and can authenticate CROs in India. The decision to check trial sites also helps the DCGI check compliance with the trial, and registration has made the conduct of clinical trials more transparent. Additionally, access to new drugs is made easy for those people who would want to participate and undergo treatment with new drugs. The evolving regulatory system may not hesitate in future to allow Phase I studies to be conducted in India for all the drugs.

There are some realities to face in terms of the rapid development of the regulatory system to match the pace at which the CRO industry is growing. Like any clinical research market, India has its own laws, rules, regulations, and guidelines that guide the conduct of clinical trials taking place in the country. In addition to internal regulations which have been put into place, the FDA has become more active in auditing clinical sites in India. The number of FDA inspections in India is still very low, but the agency is under pressure to conduct more. In addition, the globalisation of clinical research has resulted in a doubling of the number of international FDA inspections from 50 in the year 2000 to over 100 in 2007; so India can probably expect to see more.

The regulatory environment has improved dramatically in a short time period. These changes have resulted in a standardised and predictable regulatory review and approval process. There are also a growing number of FDA-compliant Institutional Review Board IRBs. To some degree, the regulatory submission and review process can be even better than other parts of the world, in that conditional IRB approval can precede Ministry of Health (MOH) approval in some instances.

A common misconception about India relates to the timelines associated with regulatory review and approvals. India is often lumped in with other emerging markets, and the assumption is that the approval process is lengthy. In fact, regulatory approval timelines are very reasonable, ranking with some of the fastest in the world. The timelines for review and approval depend largely on the type of study that is to be conducted. All clinical trials in India are overseen by the DCGI. There are two categories of clinical trials that have been established by the DCGI for the review process.

Specifically, the categories, related stipulations, and typical approval timelines are as follows:

Category A:

1. Global clinical trials with India as a location, US, Japan, Europe recognised (excludes EE).
2. Average of 20 applications per month.
3. Typical DCGI approval time: 4-6 weeks.

Category B:

1. India and developing countries/market locations.
2. India as the only location for Proof of Concept of a drug discovered outside.
3. Two Types: (1) Global (2) Local.
4. Typical DCGI approval time = 12–16 weeks.

In either case, the steps involved and timeline for review and approval have become largely predictable. Typically it takes a maximum of six weeks for a global study, with some cases taking as little as three weeks. Some studies can have their first patient enrolled within three months, with the average being not much longer than that.

Vision 2020

In the recent IPC convention, the DCGI has elaborated his plans to improvise on the existing trends. His main thrust would be to put forward suggestions on how we can harmonise our regulatory mechanisms with international guidelines in areas such as medical devices, pharmacovigilance, clinical oversight mechanisms and quality audits of clinical trials. For instance, Form 44 needs to be harmonised with the Common Technical Document (CTD). He will also be proposing a regulatory blueprint for the Central Drugs

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Standard Control Organization (CDSCO), which we are calling 'CDSCO: Vision 2020'. Since the theme of the 60th IPC is "Pharma Vision 2020: Regulation for Better Healthcare", the DCGI thought this would be the most appropriate platform to initiate an industry-wide debate on these key issues.

The 'CDSCO: Vision 2020' document will spell out the mission and goals of the CDSCO, along with the strategies to achieve these goals, with the milestones mentioned. Key topics for discussion will include the parameters for the accreditation of Clinical Research Organizations (CROs), the need for a pharmacovigilance centre in every medical college in India, the decision to put medical devices in a separate regulatory category, measures to curb the proliferation of counterfeit drugs and the framing of guidelines to regulate stem cells, radiopharmaceuticals, etc. The DCGI pointed out that the harmonisation process is already underway as members of his office, including him, have travelled to international regulatory agencies for exposure to global norms. Officials from the World Health Organization (WHO), the US Food and Drug Administration (FDA) and Health Canada have conducted 'train the trainer' workshops of zonal drug inspectors, who will in turn train their staff at the state level.

A key initiative is e-Governance, wherein a company can file, track and receive approval online. In the words of Singh, this will prove to be the panacea for the industry and the data collected will form a knowledge backbone. Starting this November, the DCGI's office will follow strict timelines displayed in the lobby of FDA Bhavan. Stressing the key role of the media, the DCGI said that the press is the connector between the industry, regulators and the public at large.

Summary

India continues to evolve and change and with that comes new myths and truths to be discovered. The growth of the clinical trials industry will allow for the realities of India to unfold to a growing number of clinical research professionals. There is an ever-increasing number of stories being told in the form of articles such as this one, and in presentations and news coverage. The drive for faster studies is forcing the industry to span the earth at breakneck speeds, and that reality will require a significant, albeit imperfect, education process. New service providers are springing up monthly. Companies, universities, and scientists are racing to record and chart the epidemiologic profile of India. Investors are pouring money into clinical research start-ups. The number of patients aware of research and enrolling in clinical trials is expanding from north to south and from east to west. These are exciting times to be forging new paths in the world of clinical research. If nothing else, the myths associated with clinical research in India will evolve, as happens in any market where industry continues to pursue the truth to successful clinical research. ■

References:

CDSCO website.

Dr. Rajam Jaishankar, did her graduation (MBBS) and post graduation (MS General Surgery) from Kilpauk Medical College, Chennai. Dr. Jaishankar has conducted a number of updates, workshops with evidence-based medicine as the theme, in the field of reproductive medicine in all most metros in India. She is the founder member of the Tamilnadu Pharmaceutical Welfare Trust and the former member of the Infertility subcommittee of the Association of obstetrics and Gynaecology. She is associated with the "Indian Fertility Society" (IFS), the National Association of Reproductive and Child Health of India (NARCHI), the Federation of Obstetrician and Gynaecological Societies of India (FOGSI) and the European Society of Human Reproduction and Embryology (ESHRE).

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Bioethics in Latin America: Development of a new paradigm (Part 1)

Bioethics originated in the USA and it was eventually adopted (and adapted) by other countries, Latin America among them. Since the bioethical discourse flourished in the North American cultural traditions, it's natural to compare it to Latin American biomedical ethics. The latter has evolved throughout 30 years since 1970, in three stages: reception, assimilation, and recreation. As a pioneer of the process by which bioethics was institutionalised in Argentina, I cannot avoid making a personal reference to my own experience as testimony and witness. Such biographical narrative concerning the emergence of bioethics in Latin America may be justified by the observation of a recognised American bioethicist that affirmed that: "identifying the source of bioethics in the USA is a subject of considerable controversy. But the history of bioethics in Latin America is, in a high degree, the story of a man."

Reception in the 70s

The 70s formed the bioethics' reception stage in Latin America. "Reception" should not be understood as a formal introduction of the discipline. It refers to how the historical and cultural situation in the region enabled or restricted the integration of bioethics. Those years have been characterised by a reaction, either of resistance or rejection, to this new movement by those who supported the civic and traditional professional ethos. As a secular and liberal morality, bioethics promoted the patient's autonomy, introducing the idea of the patient as a moral individual in medicine and emphasising the role of the patient as a rational and free agent, whose decisions are central to the therapeutic relation. These ideas were beyond the old medical ethic, paternalistic and confessional, that was still prevailing in Latin America following the authority and moral doctrine of Roman Catholicism. Doctors were used to practicing medicine in agreement with the "domination" role according to Max Weber, in which the doctor's authority is supreme and the role of the patient was to submit to it.

In the beginning, bioethics was mainly perceived as made in the USA. North American ideas, on the other hand, found resistance due to the Marxist and anti-North American attitudes that were deeply rooted in Latin America. Bioethics could not simply be transferred into the Latin American context without taking the cultural and political differences into account.

Argentina led the reception of bioethics in Latin America. The first Ibero-American bioethics programme was established in Argentina with the José María Mainetti Foundation (1969). Dr José María Mainetti founded the institute in 1972, and played an important role concerning the first bioethical activities in the region. Later on, educational programmes were developed through the Latin-American School of Bioethics directed by Juan Carlos Tealdi. Over the years, many American Academics took part in this project. The Institute has published the journal Quirón since 1970 and has produced numerous monographs on medical ethics. (1)

The Institute encouraged Bioethical Studies in Latin America under the influence of the Spanish School of the History of Medicine, led by Pedro Laín Entralgo. This intellectual headquarters brought about favourable conditions for the reception of the North American movement of Medical Humanities in Latin-American Bioethics.

The first decade of the Argentinean Institute of Medical Humanities recorded the reception stage of these disciplines, supported by the personal and institutional exchange initiated by doctor and philosopher H. Tristram Engelhardt, Jr., who by that time was at the Institute for the Medical Humanities of the University of Texas, Medical Branch at Galveston, and bioethicist Doctor Edmund Pellegrino, then Director of the influential Institute of Human Values in Medicine with its head office in Washington DC. The connection with medical humanities explains the reason why Argentina and Spain were the first countries to initiate bioethics in Latin America and Europe respectively.

The medical humanities movement, in search of medical humanism, was in line with the medical anthropology of Laín Entralgo, which school of thought I joined along with many other academics in Latin America. The reception of bioethics as a part of the medical humanities theoretical perspective meant therefore to us a critical attitude in terms of challenging unclear assumptions and value judgements, not only in medicine but also in bioethics. During the 70s, "postmodern medicine" emerged as a critic to positivist medical reasoning. These long-ranged critics affected the object, method and aim of medicine itself.

"Postmodern" medicine owes its relativism to its growing comprehensive, interpretative and evaluative nature, which is added to its reflexive condition. Thus, in Latin America we address bioethics as the new medical-humanist paradigm and as an ethic that is "implied in" rather than "applied to" medicine essentially. This ethic comes from the intrinsic axiology of the medical profession. Hence, in contrast with the North American bioethical development, which involves doctors of medicine, theologians, philosophers and lawyers, the main protagonists in Latin America of the discipline are mostly doctors and health professionals.

Assimilation in the 80s

The academic discipline and the public discourse were institutionalised within the region. Together with the restoration of democracy and the introduction of new medical technologies, such as critical care, transplants and reproductive assistance, public interest towards bioethics was expanded in the 80s. The assimilation was the reflection of the North American bioethics in two aspects: on the one hand, the increasing litigation due to malpractice in medical cases and the patients' rights movements emulated the factors that led to the birth of bioethics in the USA. On the other hand, with the restoration of democracy, a renewed interest was developed for moral and political philosophy as well as for the ideological pluralism and consensus creation, which had been by that time applied to medicine and had become the key constituents for the new bioethics.

In 1980, the Mainetti Foundation gave a boost to a second stage in the institutionalisation of bioethics in two academic areas: the Faculty of Medical Sciences and the Department of Philosophy at the Faculty of Humanities and Education Sciences at the National University of La Plata. The Medical Humanities Postgraduate office gave an opportunity for the philosophical thought of the medicine as a post-Flexnerian philosophy of the healing art instead of the reductionist model. The Flexner model comprised the old medical positivist paradigm of the medicine that was limited to the natural and applied sciences. Latin American bioethics rejected this approach and turned to a new medical humanist paradigm which used the social sciences and humanities to develop a medical theory and practice.

The last years of the decade have witnessed how the bioethics centers and institutes, along with the professionals of the discipline of the region, have flourished. The critical reception was followed by a radical period in assimilation. The radical nature of Latin American bioethics goes beyond a medical philosophy so as to turn it into a philosophy of culture and technology, passing from Meta-Medicine to Meta-Ethics in search of a fundamental questioning of the techno science. The novelty and seriousness of the problems in the current life shape a bioethical crisis from the technology era. Three new topics appear intertwined in these vital and normative crises: (a) ecological catastrophe, (b) biological revolution and (c) medicalisation of life. Bioethics was possible as a result of wider changes in our comprehension of human condition and our progressive ability to transform the human body. From the beginning, for human beings, the path of Latin American bioethics has been an interrogation in the sense of the search of the bioethics foundations in philosophical anthropology based on the new capacity to alter the body and to create a moral alternative. ■

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Tunisian Clinical Studies Watch

Tunisia is known for the well-built clinical trials system in its medical, educational and governmental institutions. Many laws and decrees have been enacted to regulate the process of clinical trials, which combine to form a comprehensive environment for fruitful clinical trials.

In Tunisia, there are different structures involved in health research governance; the Ministry of Scientific Research, Technology and Competence Development are in charge of executing government policy in the scientific research sector, as well as technological innovation and development of competence. Besides its direct tutelage on the structures under its control, it also oversees some horizontal assignments which aim to promote research in all sectors.

The Superior Council of Research, chaired by the Prime Minister, consists of representatives of the different ministries involved with research; its role is to give key direction on research in the country. At each ministry, research policy is the responsibility of the Minister, and there is formal governance from the Superior Council.

The Ministry of Public Health has created a directorate (within the General Directorate of Health) which supervises research in the domain of health, whose mission is to promote research in the sector and to assure its follow-up and assessment. The Ministry of Higher Education, through the General Directorate of Scientific Research and Technological Innovation, monitors research conducted in institutions of higher education. The Ministry of Agriculture and Water Resources supervises agricultural research, particularly in the domain of animal health and food security. Tunisia instituted the Comité National d'Ethique Médicale (CNEM) by law on 29 July 1991. Its mandate and the variety of issues for which it is responsible are modeled on the French example, whose wording is sometimes reproduced verbatim.

The Committee comprises a chair and 18 members, each of whom is appointed for a three-year term. The first issue addressed by the Committee was assisted reproduction (Avis No. 1, 1996), followed by aspects of the establishment of local ethics committees and cloning (Avis No. 3, 1997). It is noteworthy to mention that international / multi-centre clinical trials conducted in hospitals and other institutions in Tunisia require the approval of the National Ethics Committee in the Ministry of Public Health, after gaining approval from the local research ethics committee in the specific institution.

Phase II, III and IV clinical studies are performed in Tunisia, with special attention to infectious diseases with epidemic risk, chronic diseases, neonatal mortality and disability oncology, and endocrine. There are nine teaching hospital centers in Tunis; five CHU institutions and one CHU faculty of medicine in Sousse; two CHUs and one faculty of medicine in Monastir – Mahdia; two CHUs and one faculty of medicine in Sfax; two CHUs, one faculty of medicine, thirty-four regional hospitals, one hundred and twenty county hospitals, and sixty-four private hospitals.

Tunisia is known for large-scale collaboration with centers in other countries in clinical trials, including Morocco, Algeria, Jordan, Egypt, Syria, France, Spain, Portugal, Italy, Greece, Turkey, Germany, Norway, the US, Argentina, Japan and India.

The environment in Tunisia is well prepared, in terms of regulations, expertise and resources, for clinical trials. The regulations are clear, easy to follow and well-documented. Clinical research organizations in Tunisia are capable of conducting clinical trials professionally, and the existence of research projects of pharmaceutical companies in North Africa is further evidence that Tunisia is an excellent location for conducting clinical research. ■

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Re-use of Unused Investigational Products

In contrast to dealing with returns of unused investigational products (IPs) which are intended for destruction, it may sometimes happen that shipped study medication cannot be used in a certain study due to low recruitment, late stage changes of study designs or poor planning of demand for medication in certain study sites or countries. In the case of expensive study medication it may be necessary to consider re-use the distributed medication for another study site, or even another study. Proper handling and documentation throughout the distribution and re-collection process is therefore essential for assessing whether a distributed study medication is suitable, and of appropriate quality, for re-use in clinical studies.

1.General

- There should be written procedures describing:
  - the request for sponsor approval to collect shipped study medication from study sites for re-use the differentiation of study medication to be considered for re-use and return medication.
  - the conditions and documents to be available throughout the distribution chain.
  - the request for temperature monitoring and/or controlled shipment back to the distribution site.
- There should be a qualified person responsible for determining the possible re-use of Investigational Products.
- The direct transfer of study medication from one trial site to another should be avoided.

2.Decision for the re-use of IPs

- The conditions to be fulfilled before study medication can be approved for re-use may encompass the following criteria:

- The study medication is urgently needed, and new medication is not readily available (e.g. for blinded medication, un-blinding may be necessary).

- The product is generally available only in limited amounts, and/or is expensive.

- The study medication that was sent was not needed at the study site and was immediately sent back to the responsible distribution site.

- The study medication has not been handed out to a patient.

- It is proven or at least evident (confirmed in writing) that the study medication was stored under the appropriate storage conditions at a hospital pharmacy or at a study site.

- The quality has not been affected, as evidenced by factors such as:
  - the original seals have not been broken.
  - the primary packaging has not been damaged.
  - the study medication was not transported for longer than one week, and in the case of cold chain (2–8°C) medication not longer than e.g. 48 hours (depending on the capacity of the container system to keep the temperature within 2-8°C), and a written confirmation exists.
  - the transport is fully traceable.
  - visual inspection of the study medication does not exhibit any defects.
  - analytical testing of parameters such as related substances or assays do not show any degradation.

- The expiry date covers the period of the planned re-use.

- In the rare case that a study medication is to be re-used unchanged, a 100 % visual check of all packs and labels should be performed.

- Re-use of study medication should be avoided if there are doubts about its quality based on the criteria above.

3. Procedures for the re-use of IPs

There should be procedures for receiving, intermediate storage and status booking of study medication received, before it is returned into the supply chain process for another study or study site. It is recommended that Quality Control establishes a test record based on the criteria under 2., followed by release for further processing by a qualified person. ■

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As we enter a new decade of research, have our previous predictions taught us anything?

PEER REVIEWED

Originally coined by Daniel Defoe in 1726, and later used by Benjamin Franklin in a 1789 letter to Jean-Baptiste Leroy, is the famous phrase "In this world nothing can be said to be certain, except death and taxes". Until late 2007 however, those of us involved in the Pharmaceutical and Biotech R&D Industry, predictably, were certain of a few more things; that big pharma and biotech would always court and marry, and that CROs would continue to thrive and grow.

Towards the end of 2007, predictions of success lay heavily in favor of the CRO.

These companies had already proven themselves in weathering the significant downturn in business experienced at the start of the decade, and with the global economy beginning to weaken, CRO shares began to rise. Analysts believed that this was a result of the withdrawal of funds from uncertain industries and a transfer to a 'safer' CRO market, where investments would be less affected due to low risk in an industry rarely affected by economic swings. Whilst pharma was still considered to be a risky financial investment due to their reliance on the unknown success of products they research and the need for sales of those that they manufacture, CROs were considered safer in that their success is dependent only on the successful management and completion of the trials that they are contracted to perform. Add to this the continued outsourcing strategies and ongoing changes to regulations that require more trials to be conducted and you have a predicted high return on investment. And today, those in the know continue to predict that growth in the CRO market will increase by an average of 11 % a year beyond 2018.(1)

In 2008, despite the huge effects of the sub-prime crisis on the most critical industries, analysts continued to believe that the research industry was unlikely to be affected by the global crisis because clinical trials already underway would need to be completed, and new candidates will continue to enter the clinical pipeline. According to the Good Clinical Practice Journal (GCPj), "Only if things get really bad for pharma companies are they likely to cut back on the amount of clinical research they sponsor. A straw poll carried out by GCPj showed very little industry concern about the possible impact of the global financial situation on the clinical trials sector.(2)" Looking back through various articles, there have not been reports of significant job or financial losses in the research industry over the past two years. Share prices have risen and fallen, companies have downsized, outsourced, and started and stopped studies, and in a very general sense of the word, continued weathering the crisis.

So, if we seem to be "OK" from a financial standpoint, and if all predictions of future success are true, then do we really have anything to be concerned about? Financial predictions aside, whilst nearly every global industry has undergone major change over the recent decade, the research industry's methods have remained relatively unchanged. Pharma continues to be criticised for its inability to make effective new therapies for the world's unmet medical needs. Currently, the majority of pharma's income comes from products that have been on the market for many years, many of them currently or soon to be subject to patent expiry, representing a very significant loss in revenues. The existence and use of these products over the long term has resulted in a growing population of aging patients with previously fatal diseases that are now chronically manageable. This has resulted in a population that is living and working longer.

As globalisation continues, so does the change in scenery in the developing world where disease profiles are beginning to look more and more like those in the western world, thereby increasing the need for both therapies and research. And as diseases change, mutate and spread, so should the response to these diseases. The focus appears to be on oncology, cardiovascular, CNS and infectious diseases. The suggestions are that pharma should decide where to focus their efforts, be it in the continued production of medicines already on the market and the improvement of the formulations and delivery of these medicines, or in specialised therapies and new innovations. **Prediction!** It seems that the previous trend of companies merging and acquiring in order to expand market capitalisation and tackle the problem of thinning pipelines may be one of the past. According to Brian Orelli, there won't be many more large-scale mergers taking place, but rather 'smaller acquisitions and partnerships'. And the mega-large companies following their merge will have to focus on marketing rather than drug discovery in order to generate the necessary revenue needed to get the drugs they license through the extensive clinical trials and regulatory approvals process.(3) It would then only be natural to continue predicting that the need for the CRO will remain high, and with over 1000 CROs worldwide to choose from, competition will only increase, giving many of these opportunities to expand their capabilities and reach. Can we predict what the future holds for us with absolute certainty, or should we adapt to becoming a more evolutionary industry that changes with the times. PricewaterhouseCoopers (4) predicts seven major trends reshaping the pharmaceutical marketplace:

The burden of chronic disease is soaring.

Diseases previously considered acute are now becoming chronic, manageable and more global. There is an increased aging population that will continue to be part of the workforce and the value of these treatments will increase, but pharma will have to reduce prices and rely on volume to ensure that both western and developing markets will be able to afford and distribute medication. As drugs go off-patent, the need for regulation of generics and alternatives will increase, together with the requirement for research into alternative formulations, devices and methods of delivery.

Healthcare policy-makers and payers are increasingly mandating what doctors can prescribe.

With increased knowledge and technologies come better treatment protocols, self-diagnosis, and less reliance on individual prescribing decisions. Patients are turning to alternative methods of treatment, OTC, the internet and often leaving the visit to the physician as a last recourse. Industry will be forced to collaborate with policy-makers, payers and providers to ensure that they meet the need.

Pay-for-performance is on the rise.

One of the biggest challenges facing pharma is in proving the value of their therapies, showing value for money, that they work, and why a certain product is better than many available alternatives.

The boundaries between different forms of healthcare are blurring.

Patients no longer rely solely on their physician to diagnose, treat and prescribe. Despite not always being totally reliable, patients are turning to the internet and other methods for self-determination of their medical needs and thereby self-medication. As more products receive OTC status the onus falls to both the manufacturer and the consumer to become more aware and informed, and the lines between physician and patient are becoming more and more blurred.

The markets of the developing world, where demand for medicines is likely to grow most rapidly over the next 12 years, are highly varied.

As disease profiles in developing countries adapt and become more westernised due to globalisation, so will the need for existing therapies and research. Companies will be forced to evaluate their practices and determine how they fit in with developing countries where cultures, economies and regulations may be very different.

Many governments are beginning to focus on prevention rather than treatment, although they are not yet investing very much in pre-emptive measures.

Pharma is already entering into the sphere of health management and many companies have extensive corporate and social responsibility programs, as well as interests in providing training, information and empowering the knowledge of those with various diseases and conditions. But pharma will have to improve its image in the eyes of the consumer and prove that they can be trusted.

The regulators are becoming more risk-averse.

Past experiences have resulted in more stringent requirements for drug approval, and whilst approval timelines for some products have shortened, the requirement for research has increased, so it takes longer to get that product in front of the regulator.

What remains clear is that pharma and biotech will continue to court and marry, although maybe not at the same rate or scale as before. CROs will continue to thrive with continued globalisation and outsourcing, especially if pharma shifts its focus to sales and marketing. Regulators will continue to put pressure on developers and consumers and policy-makers will take a more active role in their healthcare. Here's a sure prediction for you: with continued globalisation, the need to treat worldwide diseases won't be reduced for a very long time. ■

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Russia: has all the required infrastructure and resources to conduct high-quality, accurate clinical trials.

The current regulatory framework governs the planning and the conduct of clinical trials, as well as regulating their routine control. Rules and laws secure the rights, safety and health of the patients participating in clinical trials, and guarantee receipt of reliable clinical data.

The rules governing clinical trial performance are in full compliance with international requirements. In 2005 the Russian National Standard was adopted; this Standard is in fact a translation of the ICH Harmonized Tripartite Guideline for GCP E6 (R1). The basic Russian legislation governing clinical trial conduct consists of the following laws and regulations: Russian Federal Law on Medical Products No 86-FZ, National Standard of the Russian Federation GOST P52379-2005 " Good Clinical Practice" and Ministry of Health Order No 266. In accordance with Russian legislation, clinical sites have to obtain authorisation from health authorities for participation in clinical trials. The procedure includes preparation of the submission package, comprising the clinical site's application and presentation of its facilities and intentions in terms of clinical trial conduct. One of the important factors in obtaining authorisation is the level of experience of staff. In the case of a positive decision, the investigational site is included in the list of sites approved by the Federal Health Authorities for clinical trial execution. Currently 1012 medical institutions are authorised to perform clinical trials.

Clinical trials supervision

Since 2005, Russian health authorities responsible for clinical trials supervision have conducted 153 inspections. The purpose of these inspections is to monitor compliance of the ongoing clinical trials with GCP and local regulatory requirements.

Pharmacovigilance

Russia joined the WHO International Drug Monitoring Program in 2004. The Federal Center for Monitoring of Drug Safety was established in October 2007 by the order of the Federal Service on Surveillance in Healthcare and Social Development ("Roszdravnadzor"). By August 2009, Russia had established 51 regional monitoring centres (one for each of the administrative districts). Such centres serve as a fundamental base of the Russian pharmacovigilance system. Health authorities understand the importance of the pharmacovigilance system. To this end such methodology guidelines as "Organization of the Safety Monitoring Services of the Medicinal Products at Pharmaceutical Companies or Registration Certificates' Holders" were developed. There are also a substantial number of seminars, training courses and conferences to be held in Russia.

Since November 2009, the Roszdravnadzor pharmacovigilance system has sought to monitor all cases of Suspected Unexpected Serious Adverse Reaction, which threaten patients' lives and health, and to react to them immediately. Regional Safety Centers are established either as separate units, or as structural subdivisions of the State Quality Control Centers of Medicinal Products. Pharmaceutical companies are connected to the SUSAR national registry, and can add newly identified SUSARs online. Current work to improve laws and legal acts in the field is being undertaken. Specialists in the area of general healthcare, employees of the medical institutions and pharmacovigilance staff of the pharmaceutical companies provide regional centres with updated safety information.

Timelines

As is well known, the time taken for applicants to receive clinical study approval is one of the key factors which influence a sponsor's decision to place an international clinical study in a given country. In Russia there are several steps required to receive clinical study approval. First of all, study documents should pass the expertise of the National Ethics Committee and the Russian Research Center for Expertise of Medical Products (those two steps can be done simultaneously). Final approval is issued by the Ministry of Health; it is based on the positive results of the two stages described above. Import and export licenses for the clinical trial materials (CTM) are obtained under separate procedures.

Currently there are no legally established expertise timelines. Based on experience and different sources of information, the average time period to obtain clinical trial approval is about 90 calendar days. Appropriate quality of the submitted documents is a necessary condition to keep within these timelines. Preclinical data, as well as the data of previous clinical studies, should be included in the submission package. Experts from the Russian Research Center for Expertise of Medical Products pay close attention to the results of chronic toxicity, teratogenic, carcinogenic, and other effects of the IP. If applicable, it is also vital to include in the study protocols female and male contraception methods, as insufficient description of such methods leads to additional expert queries. Though in a lot of cases delays in study approval are connected with a lack of accuracy in the submitted documents, deferrals can also sometimes derive from different administrative barriers.

National Ethics Committee

In 2009 about three thousand applications were submitted to the NEC, which is about 10 % more than in 2008. Distribution among clinical trial Phases is as follows: Phase I – 7.8 %, Phase II – 26.5 %, Phase III – 42 %, Phase IV – 9 %, studies of biosimilars – 14.7 %. Most trials are in the field of oncology, cardiology, neurology, endocrinology and psychiatry. Information on the NEC activities is openly available. Schedules of committee meetings, SOPs, committee news and quarterly reports can be found on the Roszdravnadzor website (in Russian).

Clinical Trial Approvals

The total number of clinical study approvals in 2009 was 577, which is 6 % less than in 2008, when 615 approvals were granted. The most probable explanation of this decrease in the number of clinical studies is the influence of the world financial crisis. Distribution between different types of clinical trials is as follows: Multinational

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clinical trials 62%, Local clinical trials 23% and Clinical trials in bio-equivalence 15%. Most of the trials are initiated by foreign pharmaceutical companies, with the following distribution between countries: USA 22%, Germany 9%, Switzerland 7% and UK 6%. In spite of the overall decrease in clinical trials conducted in Russia in 2009, we can see a growth in numbers towards the end of the year, which might point to the stabilisation of the situation: each quarter the amount of approvals was higher than in the previous one, as follows: Q1 -113 approvals, Q2 -129 approvals, Q3 -153 approvals and Q4 -182 approvals.

Logistics

In the context of customs procedures, 2009 was relatively calm for the clinical trials industry, though the current version of the Drug Law does not regulate the import and export regimen of clinical trial materials (CTM), a situation which sometimes causes temporary issues with CTM inter-country shipments. As an example, there were some issues connected with the importation of devices with Wi-Fi and Bluetooth (such as notebooks, smartphones etc.); however, competent legal support resolved legislative discrepancies. On November 27, 2009, the Customs Union Commission of the Eurasian Economic Community ratified Decision # 130 "On the unified customs-tariff regulations of the Customs Union of Russia, Belarus, and Kazakhstan" (coming into effect as of January 1, 2010) where the same Harmonized Commodity Description and Coding System and the same customs duty rate are used in all three countries. One of the changes deriving from this Decision will be related to the paperwork necessary for the import of investigational drugs: in addition to the previously required documentation, the importing organisation should provide Customs with documents from the manufacturer confirming the quality of the imported drug to be used in clinical trials. It is still too early, however, to estimate the overall influence of the change on clinical trials logistics.

Plans for 2010 (Inspections)

During 2010, Russian regulatory authorities plan to inspect clinical sites where clinical trials are conducted. Such sites will be located not only in Moscow or St. Petersburg, but also in different distant regions. It is planned to conduct multiple training sessions, and attestations of principal investigators and other specialists participating in clinical trials.

Regulatory changes for medicinal products

New regulatory conditions are being formed for the pharmaceutical market in Russia. One of the planned governmental measures is the organisation of the state-regulated price system, changes in state procurement policy, transfer of the local pharmaceutical industry to the Good Manufacturing Practice standards, technical re-equipment of the pharmaceutical companies etc.The main goal of this strategy is to increase the internal and external competitiveness of the Russian pharmaceutical industry. This, in turn, should increase the level of supply of modern medicinal products to the population and to healthcare institutions. Since Russia needs active development of the national pharmaceutical industry and the conditions which will allow switching of the industry to the new innovation development model, Russian manufacturers have high hopes connected with the new law.

New Draft Law Discussions

Beginning in the fall of 2009, the entire Russian pharmaceutical industry and other parties involved in clinical trials have been discussing the new draft version of the Federal Drug Law, which regulates the relations emerging from the performance of preclinical and clinical trials, quality control, efficiency and safety of clinical trials, as well as from development, manufacturing and sales of the medicinal products. According to this draft law, the current structure of the medicinal product cycle will change, and each step in this cycle (from drug development to sales, including safety monitoring) will change as well. These modifications aim to improve all the activities of the relevant authorities in the related fields. Among the positive initiatives of the draft law we can emphasise the following provisions: distinct, legally formalised timelines for medicinal products expertise and registration; introduction of the detailed procedure of drug safety and efficiency monitoring; presentation of the permanent registration certificate. New definitions, including study drug and its original substance, are introduced; the concept of orphan drugs for orphan disease treatment is also established. State price regulation procedures are detailed. Also, among the discussed issues there is a change in the procedure of state registration of medicinal products. To this end it is proposed to create a new body: a state-independent institution which should ensure execution of the Roszdravnadzor's decisions. In addition, a new state expertise of scientific validity and advisability of the performance of each particular clinical trial is introduced. This expertise will be done as a part of the submission package preparation process.

The draft law proposes to legally formalise clinical study approval timelines, which is very important as distinct approval schedule will reduce uncertainty in the overall start-up period duration. One of the possible changes in the current legislation is the tightening of the requirements of the principal investigator responsible for clinical study conduct at the investigative site. The change is that the minimal clinical trial experience of the principal investigator increases from two years (according to the current legislation) to five years. This measure might decrease the number of potential principal investigators, mainly in the distant regions of Russia: as Russia began to participate in clinical trials relatively recently, in the remote regions there is a lack of investigators with clinical trial experience of more than five years.

To discuss this and other initiatives, Roszdravnadzor engages public and pharmaceutical communities by organising open debates and round tables. Among their participants there are representatives of the regulatory bodies, pharmaceutical companies, CROs and professional organisations, such as AIPM (Association of International Pharmaceuticals Manufacturers), ARFP (Association of Russian Pharmaceutical Manufacturers), RAAS (Russian Association of Pharmacy Chains), ACTO (Association of Clinical Trial Organizations). It is too early to conclude now which of the changes will be implemented. Presumably the new law should enter into effect in March of this year, and we hope to present a report on the changes in legislation at that time. ■

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Emerging R&D Opportunities: Making the most of Latin America

Latin America is becoming an increasingly popular destination for the offshoring of clinical trials. Advantages include cost savings, availability of large concentrated pools of suitable clinical trial patients, high quality urban healthcare facilities, maturing drug development capabilities and significant commercial opportunities. However, it can also present various challenges, the most noticeable being the uncertainty around intellectual property protection. These issues are rarely insurmountable but, at the same time, companies considering conducting R&D activities in Latin America need as much information on the landscape as possible, especially at a time when the R&D environment in these countries is changing rapidly. This paper explores the landscape for clinical development in Latin America, focusing on the most popular Latina destinations for clinical trials: Argentina, Brazil, Chile and Mexico. It also raises questions as to when a company should go beyond the clinical development service model, and what criteria need to be considered in selecting a country as an option for an R&D hub.

Background

Latin America generally refers to territories in the Americas where Spanish or Portuguese are predominantly spoken: Mexico, most of Central and South America, plus Cuba, Puerto Rico and the Dominican Republic in the Caribbean. The region's population (563 million) is almost double that of North America and it is ethnically very diverse. A high proportion (78 %) of the population is urbanised, and the adult literacy rate is relatively high (91 %).

Figure 1:
Political Map of Latin America.

Economic and Political Climate

In the past, many Latin American countries have experienced frequent political change and economic turmoil. In recent years, however, the major economies of the region have demonstrated political stability and exceptional growth. As shown in Figure 2, this growth has included strong sales growth in the pharmaceutical markets (the bubble size represents the relative size of the pharma markets). Whilst the data shown includes the economic collapse of Argentina in 2002, more recent figures indicate annual GDP growth in Argentina of over 7 % every year since 2002.(2) In response to low interest rates and exceptional growth, investment in the region has been on the rise. In May 2008 Brazil's Standard & Poor's investment rating was raised to investment grade (based specifically on its economic expansion and declining foreign debt) - thus aligning Brazil with the other BRIC countries. There also appears to be a pragmatic and gradualist approach to economic policy with many countries pursuing trade agreements with Western economies; this trend is exemplified in countries such as Chile, Brazil and Mexico. From a pharma investment point of view, more centrally aligned

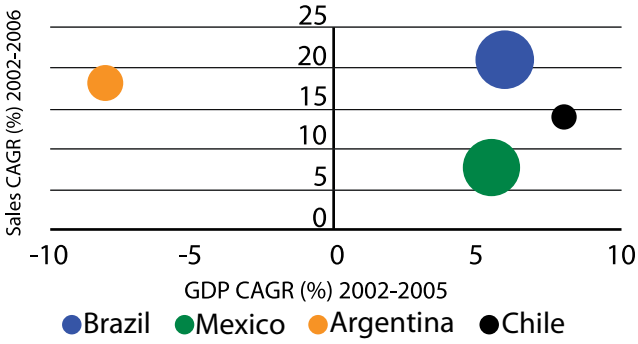

Figure 2: GDP growth vs. growth in pharmaceutical sales.

governments, strong social policies and increased healthcare spending are all good signs. The political and economic stability also bodes well for high employment rates and increased confidence in the implementation of regulatory and legal frameworks, which both contribute to a more secure IP environment.

Current R&D Activity

As shown in Figure 3, most big pharma companies already have a degree of ongoing clinical development in Latin America, with the bulk of the activity taking place in Argentina, Brazil, Chile and Mexico. The most common model is a local operating company

supplemented by CROs, the region being well served by many multinational as well as local CROs (Table 1). As is typical of most non-traditional regions, the vast majority of trials conducted are Phase 3 trials (3).

Why Latin America?

Conducting clinical trials in traditional regions such as North America, Western Europe and Australia is becoming increasingly challenging and costly, primarily due to the difficulties in recruiting suitable patients within reasonable timeframes. Four to six million Americans participate in clinical trials, and a large number of these move on from one trial to the next (4). Like many other developing regions, Latin America provides a large population of suitable potential subjects who are often keen to participate in clinical trials in order to avail themselves of free medical diagnosis and treatment which they may not otherwise be able to afford - the enrolment rate per site is on average three to five times that in the USA (5). Furthermore, once recruitment starts, the large patient pool at specific sites generally enables much faster recruitment than would be possible in many traditional Western locations. Investigators are also readily available, often keen to access new technology and become part of a global R&D community. Latin America also has several other key features which might make it a more attractive destination than the comparable non-traditional options.

Unique Advantages

High population densities around world-class medical establishments. Cities such as Buenos Aires, Rio de Janeiro and Mexico City can provide access to populations of 5 to 10 million people within a 20 mile radius4, which greatly aids the logistics of running a trial. However, the problem often cited with non-traditional countries is that patients may be not be able to afford travel to multiple sessions at clinics, and this impacts the suitability of sites for long-term studies requiring frequent visits. A highly urbanised population with a disease profile closely aligned to that of populations in the major markets of North America, Western Europe and Australia. A medical system with a strong Western heritage. Many medical professionals have at some time studied at prestigious European and American institutions. There is also good implementation of ICH guidelines and GCP standards (6,7). A common official language across most of the region. Brazil is the notable exception where Portuguese is spoken rather than Spanish. Enthusiastic investigators with excellent patient retention. At 10 %, the discontinuation rate is approximately

Country / CRO	Argentina	Brazil	Chile	Mexico
Latin American CRO Mmatiss	●	●	●	●
Thywill Latin Ame Solutions	●		●	
Latin Trials	●	●		
Quintiles	●	●	●	●
Parexel	●	●	●	●
PPD	●	●	●	●

Table 1:
Presence of selected CROs in Argentina, Brazil, Chile and Mexico.

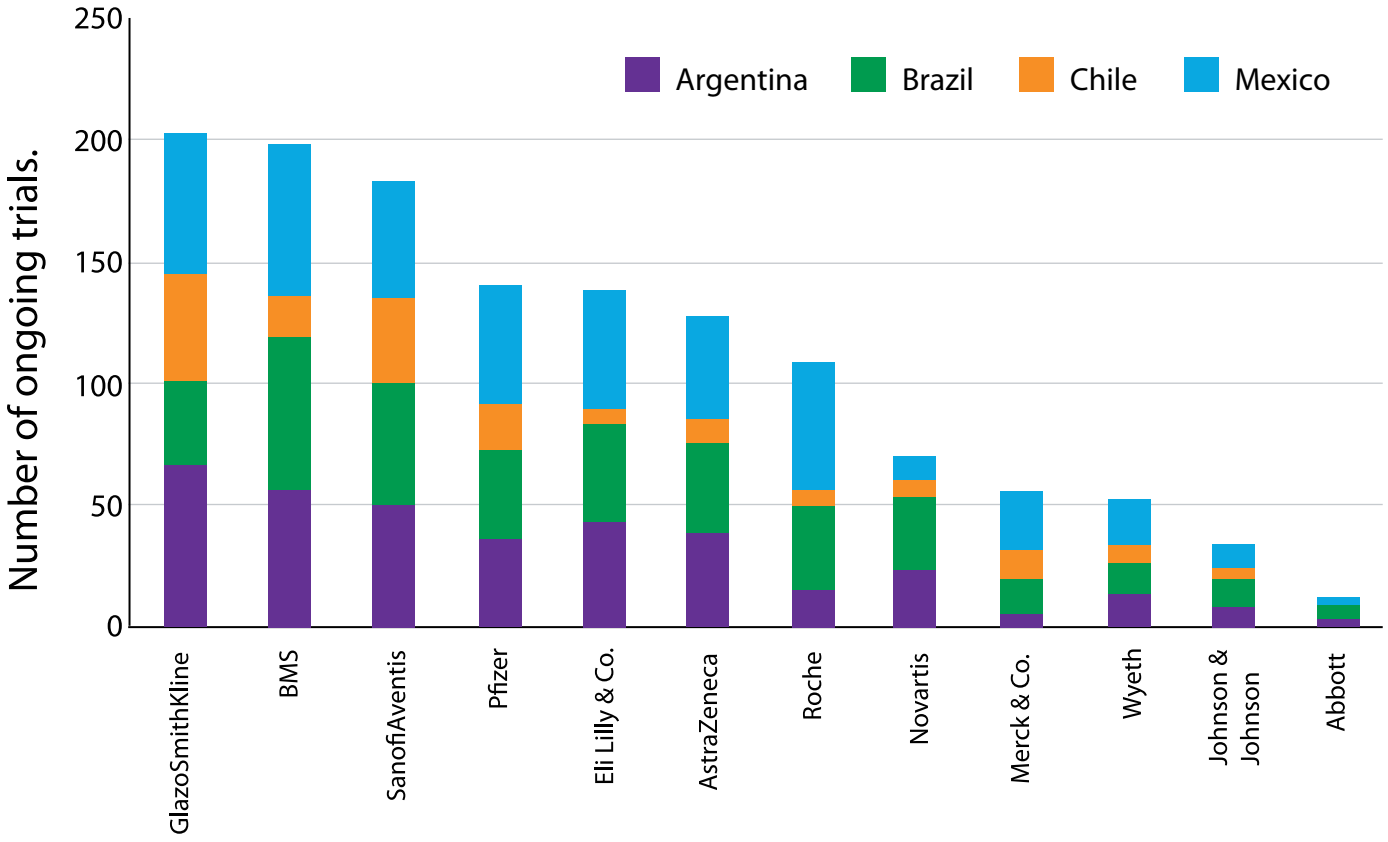

Figure 3: Big pharma sponsored clinical trials in Argentina, Brazil, Chile and Mexico in 2007. (3)

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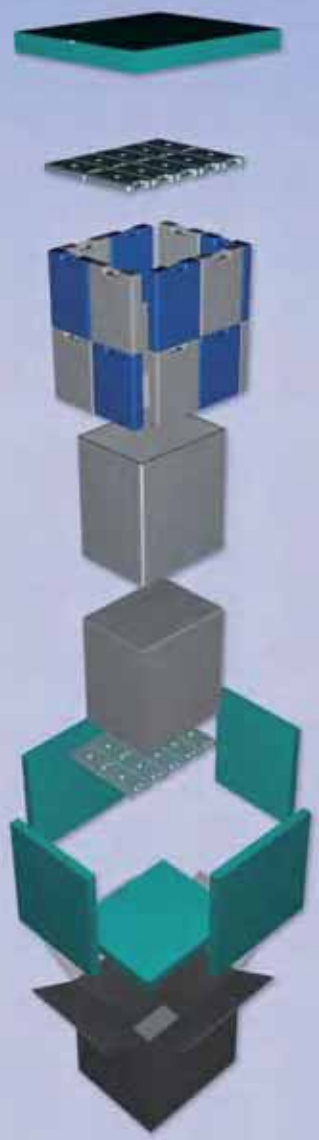

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a third of that in the USA for studies lasting beyond a year (5). Latin American investigators also claim that once a study commences, patient recruitment is faster than in traditional countries, and with an adult literacy rate of over 90%, there are few issues around informed consent or protocol compliance. Relatively low investigator and site fees. On a linear scale, principal investigator / site fee costs in Latin America and South Africa are approximately 70% of those in the USA. However, the comparable costs in India are estimated to be lower at approximately 55% of the USA costs (5). A disease profile that is well aligned with that of the major pharma markets. Table 2 illustrates the alignment of four selected Latin American markets with those of the G7 nations (USA, Canada, Britain, France, Germany, Italy and Japan), by comparing 2006 therapeutic area sales rankings.

Capability

As the region has become more popular as an R&D destination, many countries have proven capabilities. Besides the mandatory criteria for clinical trial execution, Argentina, Brazil, Chile and Mexico also have medical centres with cutting-edge technology and expertise – a significant number of these being linked to US-based institutions. However, a notable feature of these countries is the imbalance in capability between the urban metropolitan areas and the more dispersed areas. Cities such as Santiago and Mexico City have an abundance of highly-qualified medical professionals whilst rural regions may be short of medical capacity (especially personnel).

Regulatory Environment

In most countries in the region the time taken to register a drug is officially less than six months. The two exceptions are Brazil, where the time taken to register an original drug is estimated to be 12–14 months; and Uruguay, where the process can take over 3 years (2). As shown in Figure 4, the time taken to register a new drug in Argentina, Chile or Mexico is officially less than a year. Whilst these timelines seem reasonable, they are rarely met. This is often a consequence of a relative lack of resources resulting from the rapidly-expanding industry, and sequential bureaucratic processes. The regulatory processes in the three main markets are subtly different: on paper, Argentina is probably the simplest country in which to register a drug, relying heavily on FDA or EMEA reviews. In Brazil, the process can take up to 2 years in reality, and if the submission is rejected it cannot be resubmitted for a further 2 years. Mexico has recently extended its timelines to those shown in Figure 4 as a result of the increased volume of submissions. The recent appointment of the Mexican Federal Commissioner (who has a background in finance rather than healthcare) is a clear message that the main objective in Mexico is to reduce the price of medicines by promoting cheaper generic drugs - submissions also need to include evidence of local manufacturing capability or a suitable partnership.

From big pharma's perspective, the key question is to what extent timelines can be reduced through collaboration with regulatory authorities i.e. discussions around planned trials and data requirements. In many emerging markets, strong relationships and genuine collaboration based on a shared commitment to local R&D may enable local operating companies to circumvent standard sequential approaches e.g. waiting to use dossiers prepared for the FDA or EMEA. Currently this does not appear to be easy in Latin America, and it can easily be mistaken as attempted corruption. However, a major commitment may facilitate an opportunity to develop these relationships, and ultimately contribute to the improvement of the regulatory processes in the country in question.

Commercial Environment

Whilst patient recruitment, capability and the regulatory environment are all fundamental building blocks, R&D leaders should ideally also seek to optimise opportunities to align R&D activities with commercial priorities. Over 2006, Latin American pharmaceutical sales grew almost 13% compared to an 8% increase for North America. As shown in Figure 5, Brazil and Mexico are the two largest markets by sales, but between 2002 and 2006, growth of the Brazilian market was almost three times that of Mexico (see Figure 2). Argentina was the second fastest-growing market over the same period, with almost 20% growth in sales(11).

Whilst these growth rates are attractive, it is worth looking at the breakdown of sales. Sales growth in many countries can often be driven by public healthcare spending with a disproportionate bias towards generics at the expense of proprietary drugs, but as shown in Table 3, there has been strong sales growth in original brands in all of the selected countries. Furthermore, the distribution of sales across therapeutic areas in the major Latina markets is comparable to that of the US, UK and Japan (figure 6). All in all, Latin America appears to present enormous opportunity. Not only are the patients and capabilities available to conduct clinical trials quickly and effectively, but there are also significant commercial opportunities for novel, patented drugs. Furthermore, the relevant therapeutic areas are well aligned with those in the larger pharma markets. However, the region is not without its challenges.

Challenges in Latin America

The pharma industry has long held concerns over the IP situation in many Latin American countries. Argentina, Brazil, Chile and Mexico are all WTO members and are officially TRIPS compliant, but they have all been criticised for their "flimsy" IP protection record - Argentina and Brazil are still on the US Trade Representative's Special 301 Report Priority Watch List. The main issue with Argentina, Chile

Sales Rank	Argentina	Brazil	Chile	Mexico	G7 Countries
1	CNS	Alimentary tract and metabolism	CNS	Alimentary tract and metabolism	Cardiovascular
2	Alimentary tract and metabolism	CNS	Alimentary tract and metabolism	Anti-Infectives	CNS
3	Cardiovascular	Cardiovascular	Respiratory System	CNS	Alimentary tract and metabolism
4	Anti-Infectives	Genito-Urinary System and Sexual Health	Genito-Urinary System and Sexual Health	Respiratory System	Respiratory System
5	Musco-Skeletal	Respiratory System	Cardiovascular	Cardiovascular	Anti-Infectives

Table 2: Ranking of therapy areas by sales in 2006.

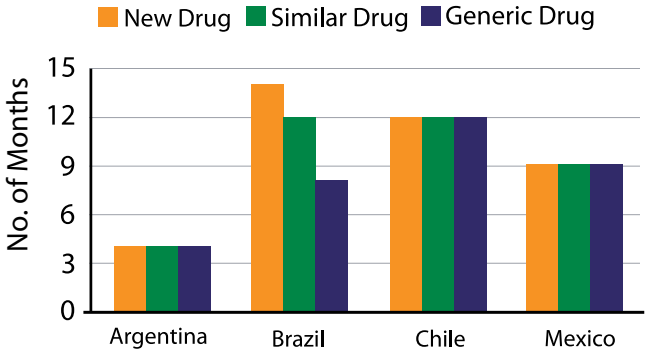

Figure 4: Time to register a pharmaceutical entity.

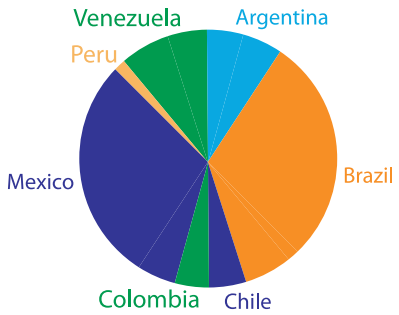

Figure 5:
Breakdown of the major Latin America pharmaceutical markets in 2006. The total value of the market was approximately US$ 21,657.

Country	Growth %	Total Sales ($m)
Argentina	12.7	454.16
Brazil	19.3	2151.07
Chile	16.0	163.73
Mexico	9.6	2679.20

Table 3: Growth of original brand sales during 2006.

and Mexico seems to be a lack of coordination between the patent-granting bodies and the authorities granting sanitary registration of products, resulting in illicit marketing of patent-infringing drugs. Furthermore, the US cites moves in Mexico (where it is in effect law) and Brazil, to allow local companies to manufacture generic versions of patent-protected drugs in certain instances where the patent owner has not started local production of the drug (2) - this latter point appears to illustrate the necessity of demonstrating genuine commitment to invest locally. Whilst the governments concerned have made various concessions and amendments to the laws, the acid test is how they handle situations where patent infringements appear to have occurred. They need to build the confidence of multinational pharma companies by demonstrating that they are monitoring and enforcing the laws appropriately, but the evidence to date is not convincing. For example: Brazil bypassed patent protection on Merck's Efavirenz and issued a compulsory license. Although the definition of a 'medical emergency', which would allow the issue of such a license, is debatable, the clear outcome from this situation was a renewed sense of discomfort amongst pharma companies operating in Brazil.Whilst Chile's favourable patent ruling over Sanofi-Aventis' Plavix (clopidogrel) in 2006 was encouraging, the fine of $25,000 did not constitute a major deterrent. Furthermore, Eli Lilly's failed legal battle in Chile over a competing insulin formulation imported from India that won a large government order does not inspire confidence. The intellectual property issues mentioned tend to present themselves downstream i.e. patent-infringing competitor compounds, but the situation does not arise upstream in discovery and early development. Could Latin America therefore not provide an option for earlier Phase work, and if so what are the limitations? No doubt local capabilities, appropriate technologies and previous experience all need to be explored in more detail.

Investment Beyond Allocation of Clinical Trials

It seems clear that Latin America provides valuable opportunities to conduct high-quality clinical trials within attractive timeframes, and many of the multinationals have been capitalising on this despite the potential challenges associated with IP protection. However, as with many emerging markets, opportunistic outsourcing without a commitment to build local capability is unlikely to be sustainable. This is primarily due to the inevitable rising costs in emerging markets and the need to build strong local relationships in order to understand and navigate the evolving legal and regulatory landscapes. At what point does a company go beyond the clinical development service model? What criteria need to be met in selecting a country as an option for an R&D hub? - i.e. a regional base with a degree of autonomy, through which local country level

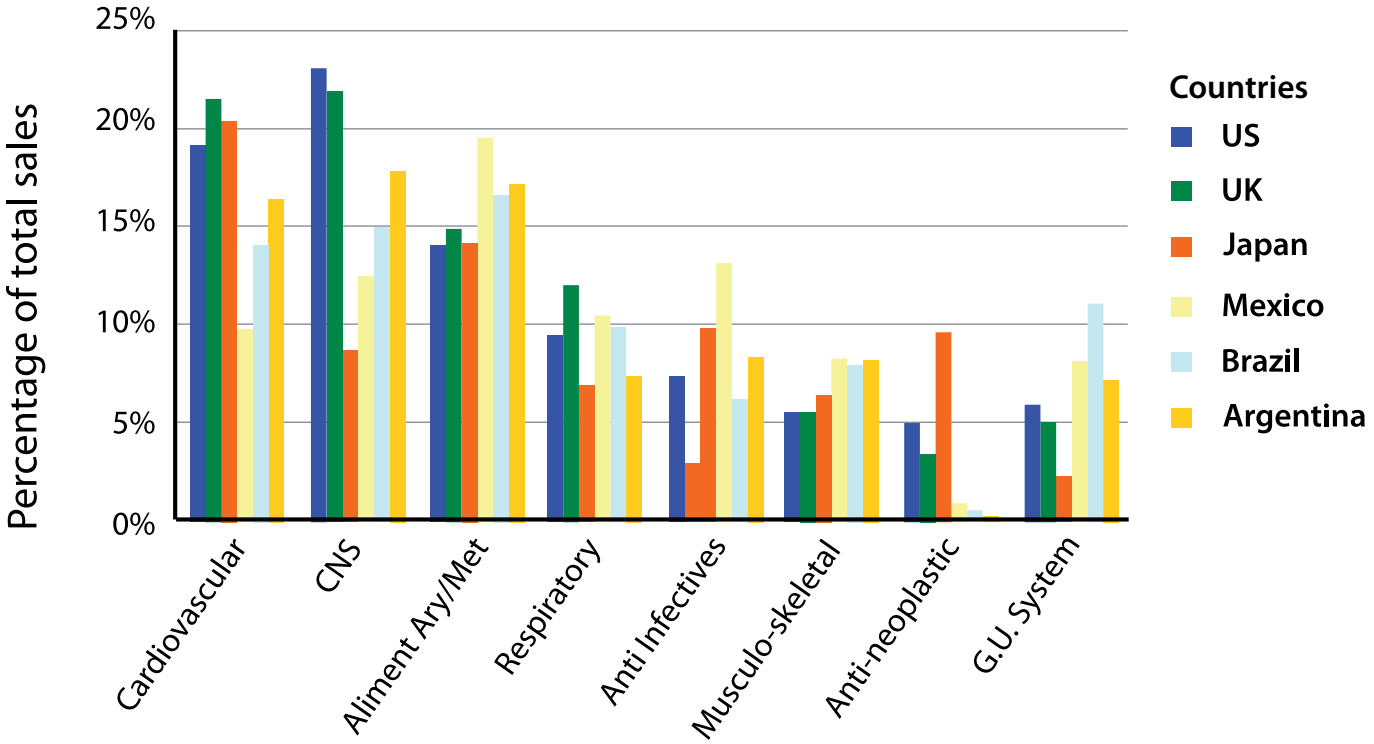

Figure 6:
Distribution of sales across major therapeutic areas for selected markets in 2006.

Similar Drugs – "Similares"

Similar drugs are products that are off-patent, but are not certified as bioequivalent to their reference drugs. They can be sold under INN or brand names.

By circumventing expensive bioequivalence testing, similar drugs can be produced extremely cheaply, undercutting generics and originals. They have long been a problem in the region, but there are concerted efforts in many countries to push them out of the market by promoting bioequivalent generics. There are however, two main challenges in doing this - the pressure to reduce the cost of drugs, and the blurred distinction between generics and similar drugs.

In some instances similar drugs would not be any less efficacious or safe than the reference drugs - the only difference is that the bioequivalence studies have not been carried out. This has often been the case in Argentina where there is no obligation to demonstrate bioequivalence of generics. However, emergence of poor quality similar drugs has led physicians to resist prescribing generics, arguing that all generics are now in fact similar drugs.

In other cases e.g. in Mexico, similar drugs are largely sourced from illicit local manufacturers or imported from parts of East Asia. They do present safety concerns and are generally less efficacious than the reference drugs. Whilst the government is pushing the substitution of patented drugs with generics, there is widespread mistrust of generics, as they are largely confused with similar drugs, which account for 60 % of the market by volume17. It is now compulsory for pharma companies to provide bioequivalency data for all medicines seeking market approval in Mexico.

Chile has also shown encouraging signs, with sales of patented drugs and licensed generics on the increase, whilst sales of similar drugs have declined steadily16. The Chilean government is also considering obligatory bioequivalence testing for generics.

operations can be supported, and through which they can feed into the main R&D centre. From Kinapse experience the following points need to be considered early on:

- Local scientific talent – FTEs and investigators.
- Current R&D activity.
- Match of pipeline to areas of specialisation in the country (recognising that whilst a country might not be of interest in general R&D terms, it might possess leading edge sites in a particular TA).
- Relative commercial attractiveness.
- Business environment – support for foreign companies, corruption etc.
- Infrastructure e.g. e-readiness, networks and airports.
- Tax incentives.
- Cost.
- Other company locations.
- Current level of activity in clinical development.
- Language.
- Readiness to demonstrate commitment to invest in in-country.

R&D capability and innovation

The logical sequence of developing capability in a region is shown in Figure 7. Given that most big pharma companies have comfortably established step 4 in Latin America, why would they invest in step 5, and which country provides the best option in light of the criteria mentioned? In many non-traditional countries the advantages of being "on the ground" cannot be overestimated, especially where the local regulatory authorities are constantly evolving and thus require skilled and knowledgeable input from in-house regulatory specialists. In moving from a clinical development offshoring model to an R&D hub, an organisation not only builds local capability, but also cements relationships with local government and regulatory agencies. It also strategically positions the organisation to take advantage of the skills and knowledge of the regional scientific community. The latter is often underestimated in these regions, particularly with regard to the potential discovery of early stage assets. The decision to develop a more established presence is subject to a number of factors, not least the economic and political outlook, which currently looks very positive in Latin America, particularly in Brazil and Mexico. It is also contingent on being able to recruit suitably trained people, and this can sometimes be a challenge in emerging markets. Latin America is not short of medics, and whilst the general availability of skills is not as high as it is in India and China, Brazil and Mexico do appear adequate in this regard.

Figure 7: Development steps in establishing capability in a region.

Conclusion

Latin America provides enormous opportunity for big pharma companies as a destination to conduct clinical R&D. However, decisions should not be driven by cost alone; a more sustainable model for the region should be built on patient availability and data quality, and it must be matched to the emerging pipeline. With large, diverse populations of treatment and trial naïve subjects clustered around world-class medical establishments, the logistics of running clinical trials in Argentina, Brazil, Chile and Mexico are favourable. Furthermore, motivated investigators and willing participants provide definite advantages over conducting clinical trials in Europe or North America. The major threat to Latin America attracting further foreign investment in pharma R&D is the lack of confidence in the protection of scientific data. Although there do appear to be progressive steps to improve IP protection in many countries in the region, the IP laws are still not always clearly enforced. Whilst this

can cause uncertainty, it can be managed to an extent by developing a better understanding and communication with local authorities (through strong local relationships), and by demonstrating a genuine commitment to the local pharma industry (through local manufacturing and commitment to developing capability within the country). The high costs implied in adopting this approach mean the pharma companies should arguably consider investing greater sums in a smaller numbers of markets, rather than the scattergun approach that many have adopted to date. Given the growth and opportunities in the region, the question is not whether to invest in Latin America, but where, and at what level. The key to success will be the willingness to invest time and energy on actually building capabilities and relationships in the region for sustainable growth and success. ■

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Regulatory Landscapes for Future Antidiabetic Drug Development (Part I): FDA Guidance on Assessment of Cardiovascular Risk

PEER REVIEWED

Diabetes mellitus is a serious disease that is rapidly assuming epidemic proportions. Huang et al. [1] recently observed that the number of individuals in the United States with diagnosed and undiagnosed diabetes will increase from 23.7 million to 44.1 million between 2009 and 2034. Additionally, the lifetime risk of developing diabetes for those born in the year 2000 is 35 % [2]. The need for pharmacologic therapies for this population is therefore considerable. However, the development of such therapeutic agents has recently attracted additional regulatory interest and, arguably, hurdles. An FDA Guidance for Industry [3] now requires sponsors to demonstrate that a new agent does not have an unacceptable cardiovascular risk. Following a brief overview of the evolution of this guidance and the resulting new regulatory landscape in the US, potential implications for the future development of antidiabetic drugs are discussed.

This article is the first in a series. At the time of writing, the EMEA is preparing an updated version of their 2002 Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus [4]. A 2008 EMEA Concept Paper discussed the need for this revision, and indicated that guidance on cardiovascular outcome studies is among the main topics likely to be addressed [5]. The updated guidance is expected in the near future, and, shortly thereafter, the second article in this series will provide a similar review of the European regulatory landscape. As and when other regulatory agencies release guidance documents in this area of drug development, they will also be reviewed.

Evolution of the FDA Guidance addressing Evaluation of Cardiovascular Risk

The FDA guidance Diabetes Mellitus—Evaluation of Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, was published in December 2008 [3]. The seminal influence in a series of events leading to this guidance was a paper that was e-published by the New England Journal of Medicine on 21st May 2007 [6]. This paper presented a meta-analysis focusing on the thiazolidinedione drug rosiglitazone. The result of note was an odds ratio for the occurrence of myocardial infarction in the rosiglitazone group compared with the control group of 1.43 (95 % confidence interval: 1.03 to 1.98, p< 0.03). Turner and Durham [7] reviewed the intense governmental and regulatory (both FDA and EMEA) activity in the days and months following the paper's e-publication, and also the controversy revolving around the scientific legitimacy or otherwise of this result. Given the already voluminous literature on this topic, this paper focuses on the evolution of the guidance and its impact on the US regulatory landscape.

On 6th June 2007, the US Committee on Oversight and Government Reform held a hearing to discuss the FDA's role in evaluating the safety of rosiglitazone (failure to adequately do so being the position of some protagonists at the hearing). Subsequently, a joint meeting of the FDA's Endocrinologic and Metabolic Drugs Advisory Committee and its Drug Safety and Risk Management Committee was held on 30th July 2007. While the committees' members eventually voted 20-3 that rosiglitazone increases the cardiac risk in patients with Type 2 diabetes mellitus (T2DM), they also voted 22-1 that rosiglitazone should not be removed from the market, therefore remaining an available treatment option for physicians and their patients. On 19th November 2007, the FDA announced that rosiglitazone's sponsor had agreed to add new information to the existing boxed warning on the drug's label about the potential increased risk for myocardial infarction. Part of the new text read as follows, and finished with a noteworthy statement:

A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared Avandia to placebo, showed Avandia to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 patients), comparing Avandia to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive.

Nonetheless, on July 1st and 2nd 2008, the Endocrinologic and Metabolic Drugs Advisory Committee met to address potential new regulatory guidance concerning cardiovascular safety assessments for all drugs and biologics for the treatment of T2DM. The committee voted 14-2 that, even for drugs and biologics that do not display a concerning cardiovascular safety signal during Phase II/

III development, there should be a requirement to conduct a long-term cardiovascular trial or to provide alternative evidence to rule out an unacceptable cardiovascular risk. The guidance resulted from discussions at this meeting. It is of note that the final version of the guidance was published quickly. It was felt that the February 2008 draft guideline on the general development of drugs for diabetes did not address cardiovascular risk in sufficient detail, and that there was need for additional guidance in this realm. The final version of the general guidance will incorporate information on the identification of unacceptable cardiovascular risk and supersede the December 2008 guideline.

Central Components of the Guidance

Demonstration is required that a new agent to treat T2DM is not associated with an unacceptable increase in cardiovascular risk. Clinical endpoints of interest include, but are not limited to, non-fatal myocardial infarction, non-fatal stroke, and cardiovascular mortality (events which comprise the Major Adverse Cardiovascular Events [MACE] composite endpoint), acute coronary syndrome, and urgent revascularisation procedures. A composite endpoint can be advantageous when the number of individual events may be too low to meaningfully compare those occurring in the test drug treatment group with those in the comparator treatment group. The guidance also makes clear that endpoints now require independent adjudication. Additional changes to development programmes going forward include the length of trials to be conducted and the nature of the subject population employed. Larger and longer late Phase II trials are called for, as are larger and longer Phase III trials that include subjects at high risk for cardiovascular events. The approach to excluding unacceptable risk can be represented by a three-component model incorporating clinical science (clinical judgments concerning absolute and relative risks), regulatory science (benefit-risk judgments at the public health level and choice of thresholds of regulatory interest), and statistical science (determining whether or not regulatory thresholds have been breached) [8]. Upon completion of a planned preapproval clinical development programme, a meta-analysis exploring the investigational drug's MACE liability is to be conducted (see Caveney and Turner [9] for a more detailed statistical discussion). Since the cardiovascular safety of the test drug is judged against that of a comparator, a risk ratio point estimate and associated confidence intervals (CIs) are of interest. Primary interest falls on the upper limit of a two-sided 95 % CI placed around the relative risk ratio point estimate generated by the meta-analysis (see Turner [8] for more detailed statistical discussion).

Three scenarios are discussed in the guidance:

- If the upper limit of this CI is equal to or greater than 1.8, a drug is deemed to have an unacceptable risk. In this case, "an additional single, large safety trial should be conducted that alone, or added to other trials, would be able to satisfy this upper [limit of the CI] before NDA/BLA submission." [3]

- If the upper limit is equal to or greater than 1.3 but also less than 1.8, and the overall benefit-risk analysis presented at submission

supports marketing approval, a subsequent step will generally be necessary. A postmarketing trial is required to definitively show that the upper limit of the CI is actually less than 1.3. Thus, for drugs that are not deemed to have an unacceptable risk at this point in time, later studies must show that a more comprehensive assessment yields a risk ratio less than 1.3. If the upper limit is less than 1.3 and the overall risk-benefit analysis presented at submission supports marketing approval, "a postmarketing cardiovascular trial generally may not be necessary." [3]

Intent and Possible Unintended Consequences of the Guidance

The intent of the guidance is to ensure that new antidiabetic drugs do not unacceptably increase the risk for cardiovascular events of regulatory interest. The importance of this intent is underscored by observations that diabetes greatly increases the risk of heart disease and stroke [10], and that the majority of patients with T2DM die from cardiovascular disease and not from their hyperglycemia per se. Traditionally, HbA1c has been used as a biomarker to judge long-term glycemic control. While compelling data from the UKPDS study showed that lowering HbA1c in patients with T2DM reduces the risk of microvascular disease [11], similarly convincing evidence for a reduction in macrovascular disease has not been provided. This has led to ambiguity concerning the exact relationship between hyperglycemia, anti-hyperglycemic medications, and cardiovascular disease. Type 2 diabetes mellitus and metabolic syndrome clearly have a complicated pathogenesis. Widely different elements and pathways have been implicated, e.g., glycerol-sn-3-phosphate acyltransferase, plasminogen activator inhibitor-1, intermittent hypoxia, and eating a high fat diet. An interesting hypothesis was provided by Stern [12], who proposed the "common soil" hypothesis as an answer to the association between T2DM and cardiovascular disease. Unlike classical microvascular complications, large-vessel atherosclerosis can precede the development of diabetes, suggesting that rather than atherosclerosis being a complication of diabetes, both conditions have common genetic and environmental antecedents. However, a unifying explanation has not yet been found. In 1990 there were only three classes of drugs for diabetes: metformin, sulfonylureas, and insulin (animal or human). Now nine classes are available [13]. These drugs attack hyperglycemia using different mechanisms of action, including modification of insulin sensitisation, insulin production, and glucose absorption blockage. Nevertheless, only one third of patients diagnosed as having diabetes achieve the American Diabetes Association goal of an HbA1c level less than 7 % [2]. Even fewer reach the target level of 6.5 % advocated by other professional organisations, e.g., the American Association of Clinical Endocrinologists and European Association for the Study of Diabetes.

The need for the continued development of new antidiabetic drugs is therefore clear. The evidence that lowering HbA1c reduces microvascular disease argues for the continued use of this biomarker in clinical trials of such drugs. In addition, regulatory requirements now also address macrovascular factors explicitly in the form of demonstrating that the drug does not unacceptably increase the risk of such disease: as already noted, this is the intent of the new guidance. However, there may be unintended consequences. The mandate of the new guidance may add tens of millions of dollars to the cost of bringing a new antidiabetic drug to the US market. While the full story is not necessarily captured by these data alone, especially given the global economic recession, inspection of relevant data on www.clinicaltrials.gov reveals a general increase in the number of diabetes trials between 2005 and 2008, followed by a levelling off in 2009. Additionally, late 2008 and 2009 saw several smaller biotech companies abandon their diabetes programmes because of the cost increase. One could speculate that the new mandates are leading all involved pharmaceutical companies, regardless of size, to re-examine their diabetes pipelines and re-forecast their predicted return on investment. With so many patients suffering with diabetes, the unclear pathogenesis of the disease, and patients not meeting professional goals for optimal care, the field is ripe for more research discoveries and the market is open for further drug developments. Regulators, policy-makers, and industry leaders will need to be vigilant and work together to ensure that the new regulatory guidance does not stifle the development of antidiabetic agents. ■

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Patient Recruitment in Emerging Markets

PEER REVIEWED

Problems with patient recruitment are universally recognised as a limiting factor in the development programme for new pharmaceuticals. Kilpatrick, Floyd & Goulson1 said that "85% of current research trials are not completed on time", and gave a number of reasons including: low subject (and referral sources) eligibility awareness, overly demanding protocol inclusion/exclusion criteria, and multiple competitive studies seeking the same population. Janet Flisak (Clinical Program Leader, Oncology at Johnson & Johnson, within the Clinical Global Operations Group) gave a specific example in an interview with Matt Buttrell2 of an instance when J&J were seeking patients for a prostate cancer study. She said the trial went to 230 sites, but ended up with only five patients – minimal results for a huge amount of effort!

All pharmaceutical companies and contract clinical research organisations could probably give a multitude of similar examples, and the literature on clinical trial methodology has many papers on various approaches to improve patient recruitment, and hence shorten trial timescales – or at least, prevent them extending even further. Conferences and seminars also address this topic regularly – a forthcoming SMI Group meeting in March, for example, has the title "Accelerating Patient Recruitment & Retention in Clinical Trials," with speakers from most of the major pharmaceutical companies and other experts in the field. Organisations are, therefore, looking to carry out clinical studies outside the traditional areas of North America and Western Europe. Some have done many successful studies in Central and Eastern Europe over the past 15-20 years, but they are now looking further afield especially Asia and Latin America, and may even be considering the possibilities of carrying out studies in Africa.

In order to find out more about what is happening in Asia I talked with Dr Roy Drucker, founder and CEO of Infinitus Clinical Research. Infinitus is one of a number of specialist CROs that are now springing up, but is unique in that it is the only Sino-Indian CRO in existence and conducts its clinical research exclusively in Asia, with offices in Bangalore (India) and Nanjing (China). Although expertise in the form of locally recruited staff with experience in carrying out clinical studies is essential, expat specialists are also required, and are being recruited through Talentmark, to ensure standards are to globally-accepted standards and to enhance client confidence.

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Roy himself has an extensive background in the pharmaceutical industry, starting with Sterling Drug Inc, and then moving to the Upjohn Company (USA), subsequently Pharmacia & Upjohn, Inc., where he held a range of posts including Vice-President, Drug Development with global responsibility for clinical drug development and medical support for marketed products. In 1996 he joined Technomark in the UK (at the time a sister company of Talentmark) as General Manager to provide services to the healthcare and bioscience industries, with particular emphasis on the pharmaceutical, biotechnology and contract research organization sectors.

In terms of GDP, China is now the second largest economy in the world, with India as fourth. China has about 1.3 billion people, with India just under 1.2 billion. There are still large rural populations in both countries, but the percentage in China (58%) is significantly lower than in India (72%). The population density in China's fertile eastern plains is significantly higher than in other parts of the country. In India, the areas with the highest population density (apart from Delhi and a few other urban areas) are in the north (bordering on Nepal) and the southwest tip. The increasingly westernized life-style in both countries, especially among those who could be considered 'middle class', means that there are growing populations of patients with illnesses similar to those found in developed countries.

In India, medical care is provided very largely by private hospitals, many of which are very basic. Many patients have to pay for themselves, although about 20% of hospital beds are available on a charitable basis. There are nearly 30 recognised languages, with Hindi dialects accounting for about 40%, and a further seven languages another 40%; the quoted literacy rate in India is about 61%. These facts give rise to a number of ethical issues as many potential patients are very stretched to pay for their healthcare and so organizers must think carefully about how to avoid making unreasonable economic inducements when recruiting patients. There is also a challenge to ensure that patients understand information given them and so can properly indicate their agreement with the informed consent document.

The pharmaceutical industry in India has been involved mainly in the development of generic products and so the understanding of the overall drug development process for new treatments or indications is generally rather weak, especially with regards to writing protocols. However, the level of knowledge and experience of GCP, especially for Phase III and bioequivalence studies, is usually very good, leading to high quality studies. One important aspect of all clinical studies, wherever they are carried out, concerns patient compliance. In developed countries it is usually necessary to depend on the motivation of the patients, but in India the cost of hiring clinical research nurses is such that it is possible to have a CRN contact each patient frequently (daily if necessary). The result is a higher level of compliance and, also, a lower drop-out rate.

A further advantage of India is that given the right type of disease, the clinical trial organiser has, Roy says, "the ability to think differently about clinical research and is able to recruit the whole patient population on day zero". This may have significant resource and organizational implications, but it can expedite the later stages of drug development markedly and can lead to a real paradigm shift in thinking.

Moving on to China. Roy noted that the recent execution of the head of the Chinese Regulatory Agency for corruption has had a salutary effect on those involved in the pharmaceutical regulation area. Approval of a clinical study usually takes about six months, with a further three months for an import licence for the clinical trial supplies. The pharmaceutical industry in China has concentrated mainly on the development of me-too products for sale in China, and so there is a complete regulatory infrastructure in place. Similarly there are many existing CROs and a Chinese GCP system, but both are geared mainly to Chinese, rather than international, requirements. Most investigators read English, but speak it poorly if at all. Overall, therefore, there is quite a lot that China needs to do if it is to be able to carry out studies consistently to globally-accepted standards – but given the current rate of progress this should happen within the next five or so years.

In China, healthcare is delivered mainly through hospitals and on the whole these are good, with plans for thousands more to be built over the next decade. There have been some moves towards private healthcare but this doesn't appear to have been very successful so far. There is no GP system in place and this makes it more difficult to get good medical histories of patients enrolled into studies. Related to this is the prevalence of traditional Chinese treatments, which may often be taken in parallel with pharmaceutical products, making it more difficult to be certain about patient compliance and, sometimes, affects the analysis of the treatment outcomes.

Roy emphasised the importance of working with organisations that employ local staff who know the language and the culture, and have a good background in clinical trial organisation and management, preferably including experience outside their home country. He also commented on some new business models which are now being explored in which local companies in India or China work to global standards on local registration of new products and have marketing rights if registration is successful, with the studies being used as part of dossiers submitted to the FDA and other regulatory authorities.

Another region with a number of emerging markets is South America although this seems to be an area which is somewhat outside the usual consideration of European-based organisations – perhaps because Latin and Central America are often handled commercially by or through offices based in North America (usually the USA). Including the Caribbean, this area has a population of nearly 600 million with about 10% of the population living in the three largest cities – Sao Paolo, Buenos Aires and Mexico City. There are 20 or so sovereign states covering an area of about 18.5 million km2. South America has two main languages (Spanish and Portuguese) but there are many other native languages and dialects spoken, and English and, to a lesser extent, French are common in the Caribbean.

Despite these commonalities the whole area is culturally diverse and ethnically heterogeneous. But it is a rapidly developing area, with improving economic status and a high population growth rate. The quality of medical care is improving and many physicians, especially those in the leading hospitals and health centres, have carried out some of their training in the USA and are publishing more papers in internationally recognised peer-reviewed journals. These facts, together with the introduction of GCP have helped ensure increasing acceptance by the FDA and other regulatory agencies of trials from clinicians in centres with a demonstrated record of good compliance.

Many prospective patients in South America are relatively drug naïve compared with those in developed countries and, also, many have no or less-than-adequate health care insurance, so that the standard of care given during a clinical trial is often higher than

they would otherwise receive. One aspect of the local culture is that in many cases the patient-physician relationship is strong. All these factors combine to give the potential for high levels of recruitment and good retention rates. A further point to consider is that although the disease pattern is similar to that of many developed countries, South America is in the southern hemisphere which affects the timing of the incidence of seasonal illnesses.

India, China and South America are definitely considered as emerging markets, but I thought that it would be of interest to look at the challenges of carrying out clinical studies in Africa, a continent where much of the pharmaceutical market is still very embryonic. I talked with Dr Trudie Lang, who was previously a biochemist with GlaxoSmithKline, and is now Research Fellow, Green-Templeton College, University of Oxford, and Head of the Global Health Clinical Trials Research Programme at the Centre for Clinical Vaccinology & Tropical Medicine in of Oxford. Most of Trudie's work is in Kenya, but the Centre also works on programmes in Thailand and Vietnam. Most clinical trials currently carried out in Africa are of treatments (mainly vaccines and microbiocides) for infectious diseases such as malaria, HIV/AIDS, and tuberculosis which are endemic, and so at this time only treatments for use in Africa can be considered for clinical trials there.

The scenario in Africa is very different to that in India, China or South America, and the organisation and funding of many studies have a direct involvement of national governments, international agencies or charitable foundations. Trials are carried out in vulnerable populations in resource-poor settings, and the end points of trials may be as basic as survival or death. It is essential to engage communities in the studies as identifying potential patients may involve demographic surveys with house-to-house visits. Local (Kenyan) staff are heavily involved in communication with community leaders including government officials, tribal chiefs and elders, traditional healers and family members, including husbands (rarely with wives). It is also important to use local research organisations, building up a long-term relationship with them. Trials based in hospitals or health centres in urban areas such as Nairobi can make effective use of local radio and word-of-mouth to help with patient recruitment.

GCP was introduced relatively recently for externally-funded studies, and is now becoming well-established. Trials must be registered and ethical approval is essential. Getting informed consent, with witnesses also involved to help understanding, can be difficult as some of the concepts are new within the African culture and, perhaps, language – Swahili, for example, has no word for 'research'. Patients receive free treatment and other medical care while on the trial. Many patients live long distances from hospitals so taking samples and getting them to the laboratory is often challenging. In some cases it may be best to take the testing technology out to a central location to minimise the need for transport over long distances.

Trudie said that the questions faced in Kenya are similar to those in other countries in Africa (including Gabon, Somalia, Sudan, Nigeria, Malawi and Zimbabwe) and in countries on other continents such as South America (Peru) and Central Asia (Nepal); but answers are being found to these questions and good work is being done. There is no doubt that the potential vaccine market in Africa and other developing countries is large, but one major future challenge will be the cost of testing and providing new-generation vaccines, which promise to be very expensive compared with existing products.

It is clear from the above that although the specific situation in each country is different, but some general conclusions can be drawn:

- There are opportunities for new clinical trial centres in emerging markets, but many centres are still in the early stages of development and need good support and careful management if they are to carry out studies to the required quality, cost and timescale.
- There are significant ethical issues in recruiting patients in very poor countries for whom any treatment could well be an incentive, and there are problems in getting properly informed consent prior to treatment.
- It is essential to use people and organisations with local knowledge and contacts.
- The implementation of ICH Guidelines and the introduction of GCP are becoming much more widespread and will increase further as time progresses.
- Each country offers an advantage over the others in some respect (e.g. the possibility of using CRN in India to ensure patient compliance; the different time of incidence of seasonal diseases in South America; the greater familiarity with the drug development process in China) so it is essential to take all the factors into account in making an informed decision as to where is the most appropriate place to carry out a specific study.

The input of experienced expat specialists is often needed to address many of the points raised above, but identifying and recruiting suitable people can often be difficult and timeconsuming – Talentmark has 37 years' experience in this area with an extensive database of high-class candidates and interim managers, and a dedicated research team to support executive search assignments.

Overall, it appears to be an exciting time as new geographical areas open up to carry out clinical studies. It is to be hoped that this greater diversity will allow the timescale of drug development programmes at least to stabilize and, for those with vision and courage, to decrease! ■

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Diabetes Clinical Trials: India & the Gulf Region

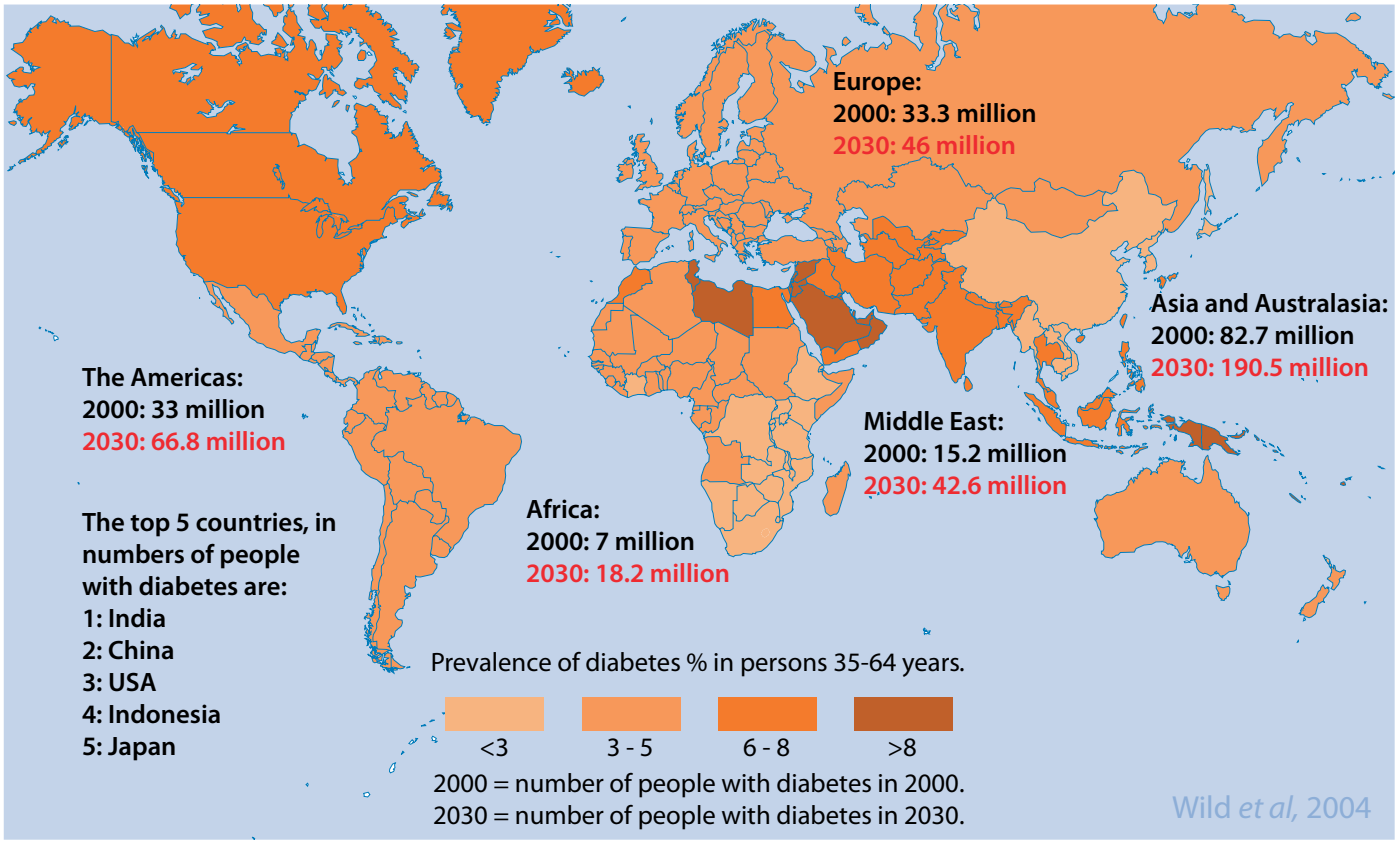
As the prevalence of diabetes grows at an alarming rate worldwide, and especially within developing economies, all initiatives with the potential to impede this growth are being considered and implemented in the affected countries. While prevention, detection and management form the cornerstones of most national diabetes programmes, a large number of clinicians and affected patients are now looking at clinical trials as an opportunity to have early access to new treatment modalities for the effective management of their condition.

India and the Gulf countries are two regions of growing concern due to their significant morbidity. While India has for several years been listed as one of the countries having the highest number of diabetic patients, the prevalence of diabetes in the Gulf countries has been significant, with more than 8% of the adult population affected.These statistics have made both regions important as destinations for the conduct of clinical trials in diabetes patients.

INDIA

India is currently reported to have the highest number of diabetic patients in the world, with the International Diabetes Federation (IDF) reporting 50.8 million people suffering from the disease. Government and non-government agencies, as well as corporate, are actively involved in campaigns that are based on community health intervention as well as education. In late 2008, the United Kingdom, acknowledging the increasing disease burden in the country, sent a delegation of experts in the field of diabetes to share expertise and collaborate with Indian institutions and companies. The last decade has seen the medical community actively developing infrastructure, resources and competencies for the management of diabetes. This has resulted in the establishment of a large number of specialised diabetes hospitals & clinics, which have helped patients to receive better care in the management of their condition. The significant morbidity, favourable regulatory reforms, and growing capabilities have all led to the inclusion of India in the clinical development plan of global pharmas targeting diabetes patients. From a couple of trials being conducted in the late 1990s, there are 28 diabetes clinical trials currently reported to be recruiting in India as per the US NIH trial registry.

These trials have not only established India as the preferred location for diabetes trials due to the recruitment potential, providing regulatory compliant data, but have also provided the patients participating in these trials with treatment options that are currently



unavailable to them at their pharmacies. The type of clinical trials that are being conducted have also progressively grown more complex, targeting the complications associated with the disease and reflecting the local clinical capabilities and expertise.

THE GULF

The recent data reported in the Diabetes Atlas of the International Diabetes Federation estimates that diabetes in the Gulf population aged 20-79 years is between 10.8 % and 14.4 % (with the exception of Iran, where the estimates are reported to be lower at 6.1 %). The highest prevalence has been reported in Bahrain (14.4 %) followed by Saudi Arabia (13.6 %). This epidemiology data makes this region relevant to the evaluation of drugs & devices in clinical trials.

While the infrastructure and medical expertise are not the same across the Gulf countries, UAE and Saudi Arabia are emerging as countries frequently included in the diabetes programmes of clinical development teams. Clinical trial regulations are evolving in the region and currently most countries do not require regulatory approval for the conduct of clinical trials, therefore approvals are primarily obtained from central or institutional ethics committees, while Phase I trials are not permitted.

The Gulf region has been involved in over 30 diabetes clinical trials in the last three years. These have included observation and mainly intervention (drug and device) trials. This emerging region shows a robust potential for the effective conduct of clinical trials due to the expanding availability of expertise, access to the large patient pool, regulatory agencies that are keen to build capabilities, and the active efforts of the pharmas and local CROs such as ClinTec International in training and developing resources to manage these clinical trials. This is reflected in the increased number of diabetes trials, from five in 2007 to 15 in 2009, as reported in the US NIH trial registry.

THE FUTURE

Diabetes has reached epidemic proportions in India, and as a result of increased life expectancy and urbanisation the number of diabetes patients is estimated to double within 20 years in the Gulf region based on WHO & IDF forecasts. While this burdens the healthcare system and would have economic repercussions, the clinical trial data emerging from these markets should help fuel the development of better products in the prevention, detection and management of diabetes in the years to come. ■

Dr. Rabinder Buttar, a highly successful British entrepreneur and the President, founder and CEO of ClinTec International. Dr. Buttar has a PhD Degree in Immunology, which she gained in 1988 from the University of Strathclyde, Scotland. Dr. Buttar served for four years on the Board of the Institute of Clinical Research (ICR UK), a key organisation for the education and development of clinical research professionals. Dr. Buttar is now an Honorary Fellow of ICR UK and a Fellow of the Royal Society of Medicine. Recently included in Real Business' List of Britain's 100 Most Entrepreneurial Women, Dr. Buttar is the recipient of a number of prestigious business awards, including the Business and Commercial Excellence Award for Northern Britain at the Lloyds TSB Jewel Awards 2008.

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Optimizing Centralized ECG data collection with NEW System Innovations

PEER REVIEWED

It has been demonstrated that some drugs can cause serious adverse cardiovascular reactions such as arrhythmias. As a result, the assessment of a new drug's short- and long-term effects on the electrical functions of the heart is a high priority in the primary stages of drug development. This assessment is achieved by performing electrocardiogram (ECG) studies. Only the most accurate and regulatory-compliant ECG data can ensure the safety of drugs.

Decentralised ECG studies are most commonly used in Phases I to IV clinical trials. However, this approach is associated with data inconsistency and inaccuracies. A centralised ECG process has been found to offer a wealth of benefits compared to the traditional decentralised approach, enabling real-time collection of dependable, quality information and ensuring accurate assessment of a new drug's cardiac effects. Most recent technological innovations have led to the introduction of new, highly compact ECG instrumentation, providing the same industry-leading performance of conventional systems at a lower cost and making a centralised approach easier to implement.

This article discusses current legislation surrounding ECG studies, demonstrates the significant benefits of a centralised approach and reviews the latest ECG device developments.

Regulatory Framework

In May 2005, the ICH E141 guideline was introduced on harmonisation of technical requirements for registration of pharmaceuticals for human use. The document provides recommendations to sponsors with regard to the design, conduct, analysis and interpretation of clinical studies to evaluate the QT/QTc interval prolongation and proarrhythmic potential of non-antiarrhythmic drugs. The aim is to identify drugs that cause delays in cardiac repolarisation.

According to the guideline, the assessment should include testing of the effects of new agents on the QT/QTc interval, as well as the collection of cardiovascular adverse events. Drugs are expected to receive a clinical electrocardiographic evaluation early in the clinical development process to provide maximum guidance for later trials. This procedure typically includes a Thorough ECG Trial (TET). If any cardiac safety concerns are raised upon completion of the TET, more robust and intense ECG collection is required to be performed during Phase III trials.

The ICH E14 guideline specifies that TET involves measurements taken by skilled readers operating from a centralised ECG laboratory. It also specifies that a clinical ECG database is derived from the collection of 12-lead surface ECGs. The quality of the ECG database depends on the use of modern equipment with a capacity for digital signal processing. By taking a centralised digital approach to ECG data collection, the TET generates highly accurate and reliable ECG data. ECG Centralisation Benefits

A centralised approach uses standardised digital ECG instrumentation for data collection and a core laboratory for centralised high-resolution data analysis. Each ECG is evaluated by a qualified cardiologist to ensure maximum data quality, integrity and consistency. The core laboratory is equipped with standard ECG instrumentation, the functionality of which has been validated, and the systems have been programmed to suit the specific demography capture requirements of each particular study.

By using digital ECG data collection systems, common transcription and misinterpretation errors associated with a decentralised approach are eliminated, accelerating the analysis process and generating higher quality data. This also solves data-variability problems from inconsistent ECG collection and evaluation methods, which are inherent in paper-based decentralised studies. In addition, many core laboratories employ systems capable of automatically checking for missing visits or changes in demography. This aids the data lock process as the study draws to a close.

When a decentralised model is used, ECG studies are carried out across multiple investigator sites using local ECG machines. The use of different instrument types at different sites leads to inconsistent results, since not all instruments use the same algorithms for calculations. A centralised process for the collection and standardisation of quality ECG data not only reduces inconsistencies that occur from site to site, but also alleviates the user's workload. ECG data management and analysis are greatly simplified, providing sponsors with on-demand, real-time access to information.

Centralisation can involve the application of best practices for digital ECG data collection, transmission and processing to enable comprehensive, regulatory-grade arrhythmia analysis. Individual safety ECGs can be also extracted and processed for interval duration measurements and cardiologist interpretation. Holter data is generated for quantifying heart rates, ventricular

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and supraventricular arrhythmias and ischemia parameters, as well as qualitatively reporting cardiac rhythm information. However beneficial the centralised ECG approach, many clinical trials still use the more traditional decentralised paper-based method. This is partly due to the common misconception that centralised systems are more expensive to implement.

The True Cost of Centralisation

Estimating the true cost of a centralised ECG approach is a particularly challenging task. This is partly due to difficulty in quantifying the number of ECGs that will need to be performed during a study programme. This inability makes it harder to project the true expenses that will be incurred over the course of the study. In addition, staffing costs, the number of investigator sites and the number of ECG instruments needed are also unknown, and normally vary depending on the specific study design. Finally, centralisation provides cost savings through the entire study management process, alleviating resources not only from the investigator site but also through the sponsor and CRO resources involved in the monitoring and data management of cardiac safety data. The cost savings in these areas as well as the expedited time to database lock have significant impact on cost reductions.

The use of a core laboratory in a centralised system is a more cost-effective approach than using multiple individual monitoring sites. Sponsors no longer suffer the burden of fees being paid to each site for technical support and qualified cardiologists. Additionally, the improved accuracy and reliability of digital ECG data collection helps sponsors reduce costs even further. By eliminating errors in collection and transcription of ECG data, sponsors can minimise the amount of retesting that must be carried out. Unnecessary over-read fees are also eliminated, and since the use of centralised equipment is an integral feature of a core laboratory, sponsors do not have to pay extra for machine rental.

Centralised ECG trials involve the rental, storage and shipping of the ECG machines to each investigator site. Conventional ECG machines can weigh anything between seven and ten pounds and be of substantial size, meaning that they can be expensive to transport and store while also being time-consuming and difficult to manoeuvre and prepare for use, especially for inexperienced users. The average rental cost of such an instrument generally varies between $100 and $150 per month. Reducing the acquisition fee, which includes the amount of rental paid for the ECG instrumentation, is one way of lowering costs.

Recent technological advancements have seen the introduction of highly compact ECG instrumentation, being just a fraction of the size of traditional systems, that will substantially reduce costs yet still provide full ECG functionality.

Optimising Centralised ECGs

New highly compact hand-held ECG devices are much easier to manoeuvre and less expensive to ship and store. Utilisation of this new technology incorporated with the process enhancements and reduced site and sponsor burden will result in significant measurable cost savings. The innovative instruments are also scientifically more consistent. They can seamlessly integrate with computer systems, enabling important information such as demographics and algorithms to be automatically downloaded in advance of a trial, thus saving staff time and costs.

Centralisation can be associated with transcription errors when conventional ECG instruments are used, producing paper printouts of all key ECG data, which are then transcribed in order for the results to be analysed. As a consequence, inaccurate results may be generated, negatively impacting the validity of the findings of a trial. Latest system innovations have eliminated the need for paper printouts by allowing data to be uploaded directly onto the laboratory computer system, eliminating errors, increasing the overall accuracy and timeliness of data, and saving staff time and cost.

It is increasingly required by regulators that ECG data are submitted to a central digital system to facilitate regulatory inspections. In that way, regulators can simultaneously access all data stored on the system and efficiently analyse data quality. Currently, this is not a mandatory requirement, however most clinical trial sponsors are trying to comply with it. Modern centralised ECG machines enable easy compliance with this request, as they store all data centrally and allow for information to be simply transferred to the database as required.

Conclusion

Although the ICH E14 guideline is not currently enforced as an industry standard, it is clear that the regulatory landscape is set to grow more complex, requiring TET studies to be performed for every new compound in drug development. In response, the industry is steadily moving away from traditional decentralised paper-based ECG methodologies and towards a centralised approach that uses digital ECG systems for recording, transmitting, processing and reporting data. Implementing a centralised approach to ECG data capture and interpretation facilitates the detection of adverse cardiac effects of drugs early in the drug development process. This minimises the risk of drug withdrawals from the market, labelling changes, and delay or denial of regulatory approval for marketing. Although centralisation provides clear advantages over the decentralised model, there is a widespread misconception that centralised ECGs are more expensive. New ECG instrumentation has been introduced to facilitate the use of a centralised approach, significantly minimising costs while increasing accuracy, reliability, usability and accessibility to quality results. ■

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The Next Generation of Clinical Supply Shipment Monitoring

PEER REVIEWED

Management of cold chain clinical supplies presents sponsor companies with significant logistical challenges, especially considering the global nature of distribution to many less developed regions and emerging markets. When investigational products are shipped, supplies are subject to various factors which may influence the way in which temperature-controlled shipping systems may operate. These variables include a myriad of external temperature ranges, supply routes, transit time, and stability of data and people. A process for efficient visibility of the success of temperature control increases detectability and therefore reduces the risk factor.

Temperature monitoring of shipments is an area in which there has been rapid development. The 'Temptale' style of device has been the most commonly used electronic monitor for many years, but a new generation of units have appeared on the market. These new monitors have improved communication methods, such as RFID or USB compatibility. They also boast more sophisticated internal and analytical software. The criteria used by quality departments to judge a product's usability, based on stability data, can be programmed directly into the monitor. This reduces the number of quality reviews of temperature excursions, while improving accuracy and turnaround times. Improved communication via general standards such as USB and the ability to program at the point of use are opening new opportunities for the development of handling the temperature-monitoring of clinical trial shipping. How can these technologies be used and are they really necessary?

Volume of Information

The volume of information flow of temperature-monitoring results from clinical trial shipping is staggering. Including all of the distribution centres of Almac Clinical Services, a conservative estimate of 60- 70,000 temperature-monitored shipments were sent in 2009, using well over 80,000 monitors as sometimes more than one monitor is included in a shipment. The majority of sponsors only require that temperature monitor results that have recorded an excursion are downloaded and returned for analysis. As an illustrative example , this would result in around 3200 monitor results being processed and reviewed per year using a sample average excursion rate of 4%. However, many sponsors now require that all monitor results are returned and archived. At Almac Clinical Services this leads to around 40% of dispatched monitors being returned, or around 32,000 results per year based on figures above.

The retention period for GMP data at Almac is ten years. Therefore, a system for handling these results must be capable of maintaining 320,000 records. Each record may contain up to 16,000 data points (the current maximum memory on most temperature monitors) giving a total potential data volume of 5.2 billion individual temperature readings. This is assuming that there is no increase in monitoring or return of temperature monitor results, an assumption which is likely to be proved incorrect if recent years are anything to go by. The monitoring requirements and return rate of the results within specification results has increased year on year since 2005. The volume of information from temperature-monitored shipping is set to increase for the foreseeable future.

Speed of Return

Time is always precious when distributing clinical supplies. Depending on trial design, the potential impact of a delay of available drug at a site can range from an inconvenience to the study subject, to lost enrolment in a trial, or even missed patient dosing in the most extreme case. A shipment arriving with a temperature excursion showing on the temperature monitor cannot be administered at the site until the recorded data has been reviewed by a delegated individual. This individual is almost always not at the site or even in that country. Getting the data from the consignee who receives the shipment to the individual who will review the data as quickly as possible is critical.

The majority of monitors currently used to record temperature during transport that can be reviewed at a later date require specific hardware to access the results. The monitors must be returned to a central location for downloading for the result to be linked with the shipment information and then sent to the individual responsible for the review. This can be a lengthy process if the shipment has been delivered to a remote location. A typical time for the return and review process is five days, and it can be as much as two weeks. For the duration of this period the shipped product is not able to be used at the site, and takes up valuable temperature-controlled storage space. Meanwhile a patient dose or enrolment may be delayed for a similar length of time. In this age of high-speed data communication, why are we shipping temperature data round the world on small electronic devices with a clear negative impact on efficiency of a study?

Low Speed, High Cost

The length of time taken to communicate the results of shipping temperature records can be detrimental to a trial or patient. It also has a high cost. The courier charges on a monitor return range from £30 or so with an express courier to hundreds of pounds from the most remote sites. A conservative estimate for illustrative purposes is around £45. For example - a study requiring 750 shipments, based on the increased trend for 100% return of all monitors regardless if the shipment has gone out of specification , we would estimate @40% return rate. Avoiding shipping costs associated with returning these devices would save £13,500 across the 750 shipments. This may not seem a very significant cost in terms of a clinical trial, but this is just to move a string of numbers from one location to another. The total cost of report compilation and review in terms of lost time far outstrips the return cost.

The cost of report compilation and review in a trial involving 600 shipments from UK to Spain has been estimated at 2,304 staff hours (Cold Chain to Clinical Site: The Shipping Excursion. Ray Goff, Pharmaceutical Outsourcing, Vol. 9, Issue 4). These lost time hidden costs are often overlooked and not factored in to the overall cost to a trial. A streamlined method of result communication has the potential to reduce the monetary costs of returning monitors to base, as well as time invested in staff hours.

Practical Improvement

Almac Clinical Services decided it was time for a change in temperature monitor results handling. There are certain key areas that were most suitable for radical review:

- Return results to base without physical return of the monitor.
- Streamline the communication routes.
- Support review of excursions for product usability.
- Support archiving of GMP data.
- Enable effective KPI review and process improvement.

The system that was previously in use was sufficient, however we had the opportunity to replace it with a purpose-built system that is ideally suited to management of multiple clinical trials from very large to very small, and offers the full range of services that our clients wanted. The end result was the Shipping Temperature Electronic Monitoring System (STEMS).

The first obstacle that had to be overcome was getting the monitor results returned to Almac Clinical Services without having to send the monitors back using an express courier. Not only does this add time and cost to the process, the consignee also has extra effort to arrange the collection with the courier. Online collection of data has been available for some time using USB-enabled devices. It was decided that this would be the main method for data collection as it

was established and intuitive to the end user. Now the consignee is able to take the monitor to their computer and upload the results to our server without the need for any dedicated hardware or software. Nothing could be simpler or faster.

As soon as the information from the monitor is on Almac Clinical Services' server, the streamlined communication is straightforward. All the predefined interested parties are immediately notified of the results of the temperature monitor. This means that any required corrective actions can be started at the soonest possible moment. Similarly, for shipments that arrive within temperature specification, recipients of the notification can have that warm fuzzy feeling knowing that everything has arrived ok and to plan. This communication process takes the old model of following up after an event has occurred, to the new model as close to a live system as is practical in airfreight temperature-controlled shipping.

The notification of an in specification shipment is nice to have, however, where there has been an excursion, there must be review of results and a decision made on the usability of the product. The excursion could have just skimmed past an upper or lower limit for a fraction of an hour, or could have been exposed to extreme temperature in some handling error, for example. Determining how significant the temperature excursion during transport was, and whether it negatively affected the product, are now the primary goals of the clinical trial project managers. The decision-making process for temperature excursions is usually restricted to a specific group of people who have the necessary training and knowledge to make the decisions. Therefore, only a restricted group are allowed access to the specification reports to review the data and record whether the product within a particular shipped box is usable or not. This trained group of individuals are notified to log directly into STEMS, and from there are able to review all the recorded temperature data, enabling them to make a decision on the usability of the product. The decision is then recorded and archived in STEMS. Notification of this decision is essential and requires immediate communication in the same way as the communication of the in spec/out of spec status. Again, the people who need to know are immediately informed automatically by STEMS.

The net result for an individual shipment that has had a temperature excursion recorded during transit is that the monitor result is sent to the responsible individual and reviewed for impact on the product. Notification of the decision made is sent out to the people who need to know urgently. All of this can happen within minutes of the shipment being delivered. This is a giant leap forward from the previous process that would take anything up to several weeks depending on compliance. The STEMS process enables super-quick communication of results in a fully validated, 21 CFR Part 11-compliant system.

The communication of shipping temperature results and review of excursions covers the in-line part of the process. The new STEMS system also provides effective archiving and trend analysis tools. Archiving information is a critical part and legal requirement of running a clinical trial. Confirmation of the shipping temperature conditions can be very useful, for instance at the end of a study when returned stock from sites may need to be used for another purpose, such as continued compassionate use. A full temperature history of the specific product is the best way to be sure that it has not been negatively affected by extreme temperature during its lifetime.

Trending of temperatures during shipping opens up a whole area of process improvement. The actual readings can be reviewed over time on specific transit routes to assess whether the risk of excursion is too high with the current method of control. Processes can be adjusted in response to this information, then the impact of the change can be quantified by the readings subsequently recorded in the system. Couriers, insulated shipping units, airlines, customs, weekdays, even individuals, can all be reviewed and analysed for trends and potential improvements. Add in a root cause tool and there is no end to the level of insight into the strengths and weaknesses of the temperature-controlled supply chain. The information gathered by STEMS will be more than just an archive of results; it will drive the future development of Almac Clinical Services' temperature-controlled shipping solutions.

Temperature monitoring of clinical trial shipping is a fast-changing environment. The demands from sponsors on monitoring requirements are ever-increasing, demanding more detailed monitoring and faster access to results. Ultimately the prime goal of all this caution around temperature monitoring is to protect the patient enrolled in the trial, and to protect the trial to give new effective medications the best chance of getting to market for future patients. At Almac Clinical Services we are striving to make the process of temperature-monitored clinical trial shipments safer, faster and more efficient. STEMS is the next step in our journey towards total temperature control. ■

Nathan Kohner obtained a BSc (Hons) degree in Mathematics at Edinburgh University. He joined Almac Clinical Services Temperature Controlled Distribution Team in 2005. Since then, Nathan has been a driving force behind, Almac Clinical Services temperature -controlled shipping strategy and was responsible for the introduction of the QB shipping system and designed the Shipping Temperature Electronic Monitoring System (STEMS). With his background and experience, Nathan often lends himself as a guest speaker at key pharmaceutical and biotech conferences.

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Consolidating Your Language Outsourcing for Global Clinical Development: A Roadmap from End to End

The role of the language services provider (LSP) in clinical development is changing. Traditionally, sponsors and CROs only contracted the services of an LSP when an immediate need arose. While this method evolved out of necessity, its shortcomings are clear: high prices, excessive delays, and poor quality and consistency — all of which can lead to increased patient risk. Today, however, the world's best LSPs are better positioned than ever to serve clinical development clients with end-to-end, multidimensional language solutions.

As more and more clinical trials are being conducted internationally and the clinical development world becomes increasingly dispersed across the globe, it also becomes more competitive. Therapy-developing companies who take a measured and consolidated approach to language outsourcing will earn an edge in a number of areas, including consistency, speed, cost, risk management, and regulatory review. Despite these benefits, many organisations have found it difficult to make the transition to a consolidated model. Companies involved in clinical research are often, both knowingly and unknowingly, using dozens or even hundreds of LSPs or linguists for their clinical trials. How is this possible? With strategic partnerships ruling today's clinical research environment, the lack of central decision-making is the primary contributing factor: sponsors partner with CROs, CROs partner with in-country representatives and agencies, and in-country agencies partner with subcontracting linguists, and so forth. This occurs for a number of reasons:

- Global trials are often decentralized, and different offices or locations have existing relationships with local providers
- There is a perceived convenience in pushing the translation procurement responsibility downstream to a CRO or an in-country partner
- Many incorrectly assume that there is a quality benefit achieved by completing translations in-country.

By taking a panoramic snapshot of what a consolidated end-to-end solution would look like in the context of a general clinical development timeline, this article presents a roadmap to follow, whether you seek to supplement your existing global initiatives or fully transition to a consolidated approach.

Q: WHY CONSOLIDATE?

A: Improved Quality and Consistency Through Centralised Translation Memory

Every single LSP you work with should be maintaining an evolving Translation Memory (TM) and style/term glossary. (If you have any LSPs that aren't offering these, they should be the first to go.) Your TM and glossary are living documents that capture your translated language and store your stylistic, linguistic, and branding preferences to be used on future projects. During the translation process, documents are analysed against your TM for segments of text that match exactly to previously approved translations (100 % match), as well as segments that represent a near-match (fuzzy-match terms). With a properly built and used TM, these segments are incorporated automatically.

In a decentralised vendor environment, each LSP holds a different TM (or sometimes no TM at all), which negatively impacts translation consistency, and this gets worse over time as subjective discrepancies accumulate. By consolidating to a single partner or a small, trusted group, you can guarantee that all projects reference your organisation's unified TM and glossary, and you can immediately reap the quality and consistency benefits associated with a managed, core terminology database.

Cost Savings

The heightened budgetary oversight a centralised approach offers has a direct positive impact on costs. Sponsors often get bills from CROs with a single line-item charge for translation. Likewise, CROs get similarly general bills from in-country partners. There is no way to know the exact details of the charges, such as per-word rates, TM usage, possible service mark-ups, or even which LSP is being used. Furthermore, by cutting down the number of LSPs you use, the quantity of work you send to each provider in turn increases. You are therefore in a much stronger negotiating position to seek volume-based discounts and partner-inclusive preferred pricing. By consolidating, you can negotiate a global pricing contract that extends to all of your partners and requires that all translations reference your core TM, resulting in a higher proportion of matching text. You are now passively (by monitoring itemised translation spend and TM statistics) and actively (through global contract negotiation and improved TM statistics) reducing costs.

Expedited Timelines

Time savings are particularly critical given the value imperative of time-to-market in clinical research. With the cost of developing a single biopharmaceutical product averaging over $1.2 billion USD(1), expedited timelines allow you to get your product to market as quickly as possible, and thereby increase ROI. When you utilise a centralised TM, the ratio of matching text leveraged against existing translations is far greater, meaning fewer words will require time-consuming and costly human translation. Furthermore, when

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your terminology is dependably consistent with past documents, the amount of time spent on reviews and revisions is significantly reduced.

White Paper:
HOW AN END-TO-END LSP ALLIANCE FITS
WITHIN THE CLINICAL TRIAL WORKFLOW

While every clinical development programme is different, we'll use a general framework to illustrate the full potential of a consolidated LSP approach.

Pre-Clinical and Phase I Development

Traditional document translations are the most common need in pre-clinical development and Phase I trials — you may look to your LSP to handle documents such as research papers, patents, and pre-clinical study reports. While documents may reference the same trial, each class requires distinct subject-matter expertise. Your LSP should assign patents to a linguistic team with legal expertise, while pre-clinical study reports should go to a team more versed in the appropriate scientific terminology. At this early stage, it's important to realise that you have begun the process of building your active TM and glossary with trial-specific terms that will be needed to maximise translation consistency throughout the development lifecycle.

Phase II and Phase III

In Phase II and Phase III trials, the role of your LSP becomes more complex and your needs will expand beyond document translation alone.

Patient-Facing Elements

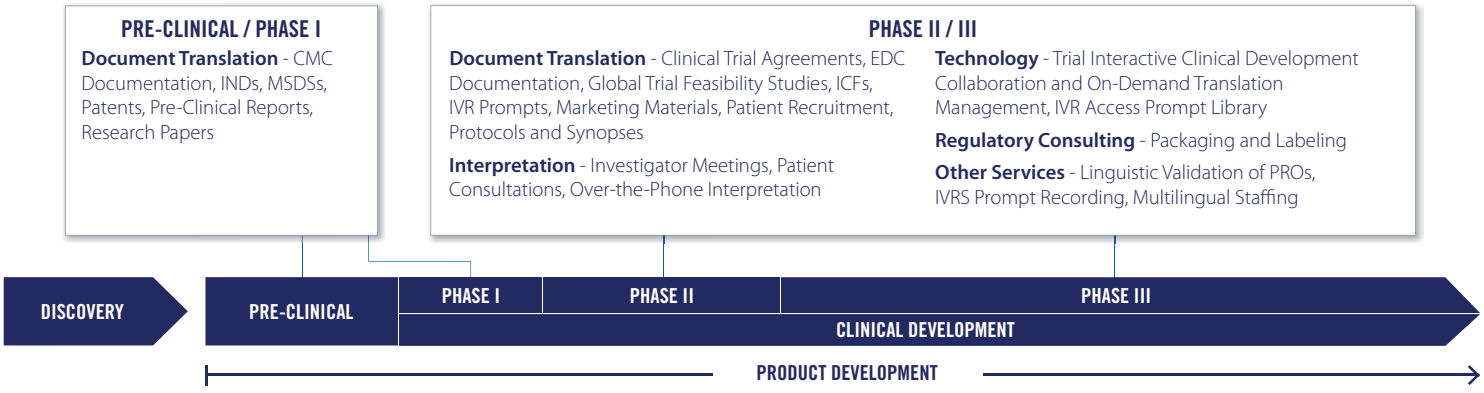
In conducting a global trial, LSPs play a central role in ensuring that you present accurate information to patients at investigative sites around the world. From patient recruitment strategies leading all the way up to meeting with personnel at investigative sites, study subjects are keenly aware of whether a company is or isn't truly investing in developing therapies for their particular disease indication. Vital documents like informed consent forms (ICFs) must be translated appropriately and can't appear to be choppy, word-for-word adaptations from an English source. This is imperative both for maintaining credibility with patients and for meeting the rigorous requirements of each country's ethics committees. Native-speaking interpreters or full-time staff members may become necessary to conduct patient interviews or simply to assist investigative site personnel with a multilingual population. Also, in instances where face-to-face interpretation or a local staff member is unavailable or impractical, over-the-phone interpretation (OPI) services, while not an equivalent substitute for a face-to-face interpreter or native-speaking investigative site personnel, are a valuable and cost-saving tool to have at your disposal, particularly given the fact that the best OPI providers offer connection times of less than 30 seconds.

Patient-Reported Outcomes

With Patient Reported Outcomes (PRO) measures becoming almost a mandate in global clinical trials due to FDA and other regulatory Guidance Documents(2), ensuring that questionnaires and scales are properly linguistically validated is crucial. As the acceptance of this data hinges on your ability to show that the instruments are equivalent across all study populations, every available precaution must be taken to ensure a reliable process is applied. This means that linguistic validation must be considered an entirely different process, or even a separate practice area, from standard document translation, and that a documented and proven methodology specific to PRO instruments must be in place.

Investigator-Facing Elements

While many translated documents are for patient use, your LSP will also be tasked with translating investigator-facing materials such as study protocols and protocol synopses, investigator brochures, and clinical trial agreements; for each they will draw on your translation memory for existing terminology and then add newly translated text into the TM to be used in the future. Interpretation on the investigator side is common as well, as you will likely have multi-country investigator meetings; or perhaps you will present your data at therapeutic medical symposia that require standard consecutive or conference-style simultaneous interpretation. While it may seem logical to enlist an event planning service for these meetings, those services often outsource the interpretation component to an LSP with a hefty markup.



Interactive Voice Response Systems (IVRS)

It's not difficult for an LSP to make a case for their ability to translate IVR prompts. However, an end-to-end partner can take your source-language scripts and complete translation, voice recording, and testing, and then deliver system-ready prompts with little to no client involvement. Furthermore, if your LSP offers an organisation and storage solution for translated prompts, you're ensured of never having to record the same prompt twice. Since organisations often utilise prompts across multiple trials, having access to all prompts represents an immediate return on investment for your LSP relationship.

Regulatory Review and Phase IV

In Phase IV, compilations of documents into eCTDs and MAAs/NDAs may need to be translated. For EMEA submissions, you may need to comply with PIM or provide translation with XML output. In addition, standard document translation is required for materials like batch records and manufacturing documentation, and all benefit from drawing upon the existing TM to maximise consistency with documents translated earlier in the trial.

While most LSPs are great at fulfilling requests for packaging and labelling translation, in some cases it might not be entirely clear how to request translations in the first place, given the sometimes differing requirements from one international market to the next. A good LSP can offer regulatory consulting services that take this knowledge burden off your employees and guarantee that your work is done exactly the way it needs to be done.

Commercialisation

When the time comes to expand your advertising initiatives to international markets, whether your campaigns are managed in-house or through an agency, simply translating the material from one language to another is not a winning game plan. For a number of social, political, cultural, and linguistic reasons, concepts don't perfectly translate from country to country. Since one primary goal is to produce global campaigns that read as if they were originally conceived and written each respective country, qualified LSPs understand that making a mistake can have potentially catastrophic – and often well-publicised – results.

Since "word-for-word" translations are not an option in marketing campaigns, agency-style services such as in-country market research, focus group assembly, copy adaptation, and cultural consulting can be helpful. And if you prefer to work through a healthcare marketing agency, you need to take extra care to maximise the success of your global initiatives. The only way to guarantee the standard of service from a third level of vendors – LSPs in this case – is to screen the vendors yourself; you should require your agency to work from an approved list of vendors when outsourcing multilingual work. This approach actually makes the agencies' jobs easier, as they are not burdened with vendor selection and rate negotiation, and they can proceed freely knowing that they are working with a partner already approved by their client.

White Paper:
DEFINING AN END-TO-END PROVIDER, AND

HOW TO CHOOSE AN LSP

With such a strong case for LSP consolidation and a clear picture of how an end-to-end partner fits into the clinical development lifecycle, the final item to explore is how you would go about selecting and forming the ideal LSP partnership.

Quality System Certifications

Many factors will contribute to your decision-making process, but the number one consideration must be quality. Size, speed, and pricing are important elements as well, but all are of little value to clinical development if not combined with a quality end-product. First and foremost, a quality-focused LSP will be certified to industry-recognised standards. The two most applicable standards for quality control in the language services industry are ISO 9001 and EN 15038:2006. The former has been around for quite some time and is likely familiar to most in the clinical world, and while not a translation-specific standard, its stipulations for process management, continuous improvement, and customer satisfaction are nonetheless extremely valuable to an industry whose pursuit of quality is ongoing.

The shortcoming of ISO 9001 specific to LSPs is that its primary areas of focus – process and service – do not specifically address quality for translation. Accordingly, with the goal of authoring a global standard specifically addressing translation quality, the European Committee for Standardization has published EN 15038:2006. Though born in Europe, EN 15038:2006 is a globally applicable standard, and it considers project management, technical and human translation resources, and the actual translation and review process. There is a newly-minted American counterpart, ASTM F 2575-06, but it functions more as a guide than as a true standard. While ASTM, similar to EN, addresses translation-specific subjects, there is no official process for becoming certified to its provisions. LSPs can claim compliance, but without a third-party certification those claims are not verifiable.

Figure 1:
Process of clinical developement and outsourcing.

Linguist Screening and Subject-Specific Expertise

A major limitation in the LSP industry is that there is no central, unified body responsible for certifying linguists' abilities and subject-specific expertise. For clinical development, it is critical that you devote part of your vendor qualification process to exploring exactly how linguists are identified, screened, and evaluated, both initially and on an ongoing basis. Important qualifications include linguists' native-speaking language backgrounds, years of experience, and documented expertise in specific areas pertaining to clinical

development. And don't assume that in-house linguists are always best; while they are typically skilled linguists, they often possess only generalist-level industry knowledge so that their employers can use them on as many projects in as many industries as possible.

Beyond Traditional Translation Memory Tools

The human role in translation remains the backbone of the language services industry, as we're still many years away from having reliable machine translation technology. It's important to distinguish, however, between machine translation and computer-assisted translation (CAT) tools. Given the rudimentary nature of the existing machine translation technology, it cannot be considered a viable option in the context of clinical development. Computer-assisted technology, however, (which includes TM) is an absolutely indispensable ally. It's easy to think of TM as a black and white concept, as the long-held advice has always been to ask one of a couple simple yes/no questions of potential LSPs: "Will you be using TM tools?" or "Do you have a TM glossary for us?" These questions and conclusions ignore a fundamental flaw in the system — your TM is only as useful and accurate as the translations used to create it and the degree to which it's maintained and referenced. Without a reliable TM and glossary, even the most capable translators in the world are not privy to your specific stylistic preferences or corporate terminology choices. A simple mantra that you should follow is: "The more access, the better." Simply put, you will get the most out of your LSP relationship, and in return your LSP can provide you the best level of service, if you assume an active role and have the tools to maximise your involvement in the relationship. The two components of TM and glossary access that you should consider are first, the ability to easily review, edit, and update your TM and glossary, and second, the way in which these changes are made.

White Paper:

Traditionally, TMs and glossaries have been built, maintained, and updated at the desktop level by each LSP. To make edits, you have to request the file from each LSP, make your changes, and send them back to the vendor, hoping your changes are implemented properly. New technologies allow your TM (which should be your company's intellectual property) to reside on an LSP server, making it accessible from anywhere, by anyone, and at any time. You can designate access privileges to your reviewers as well as multiple LSPs, which universalises consistency across your documents even when more than one vendor is involved. Language solutions have come a long way from the days of basic desktop TMs that captured matching text strings on a document-by-document basis — there are now robust technology solutions available that give you unprecedented access, control, and ownership over your TM, and the world's best LSPs should be offering these to you.

Emerging Workflow Technologies

Since large clinical trials can involve upwards of 50-100 daily translation requests worldwide, technologies that streamline document submission and delivery and track project status and costs, are key to a successful centralisation plan. In many cases, new technologies like online web portals and virtual data rooms have replaced email as the preferred medium of file transfer and collaboration between client, LSP, and reviewer due to the workflow efficiencies they offer.

As communications migrate to electronic solutions, security is vitally important, as even the most user-friendly interfaces and seemingly useful solutions are of no value if confidentiality cannot be guaranteed. Secure online workspaces promote open document exchange, communication, and transparency between internationally dispersed stakeholders, which maximises collaboration between sponsor, CRO, and investigative sites.

Vertical and Horizontal Scalability

The final element to look for in an end-to-end provider is vertical and horizontal scalability. Vertical considerations, since you will now be looking to one or several vendors to handle a quantity of work that was once dispersed among many, ensure the volume of available resources is sufficient. Horizontally, there are numerous specialised needs beyond clinical documentation, such as legal contracts and agreements, training/e-learning, subtitling, voiceovers, or even website localisation.

If at any point you encounter a project with a volume your LSP can't handle or in a subject area your LSP doesn't serve, you've essentially forfeited the consolidation benefits you'd worked so hard to secure.

Conclusion

Consolidation of language solutions in the clinical development world should be viewed as an absolute necessity and a quality mandate, which just happens to facilitate some key financial and time benefits. By exploring the case for consolidation, seeing how an end-to-end solution might look within the context of a model clinical development programme, and considering the various data points that define a comprehensive LSP, this article has provided the basic tools you can reference to secure key competitive advantages for your company. Not only will you realise an immediate improvement in the quality and consistency of your translated work, but a close LSP alliance streamlines collaboration and organisation, saves money and time, and most importantly, instills among all stakeholders the confidence that these important and sensitive materials are handled by a partner that can be trusted. ■

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Effective Management of Clinical Trials Supplies in the new world order of global studies

Ever since the first Clinton administration placed healthcare reform at the top of its agenda, governments worldwide have stated and restated their commitment to controlling spiralling healthcare costs, which in the US alone have increased from 5% of GDP in 1960 to 16.5% in 20061. It's a highly complex and emotionally-charged debate, influenced by factors ranging from increased life expectancy to technology and medical insurance costs.

Caught mid-stream in the debate is the research pharmaceutical sector, targeted on the one hand as a major source of cost, yet tacitly expected on the other to continue advancing medical science via their R&D programmes. With the average cost of bringing a new drug to market estimated at GBP 570 million, the costs are indeed significant - yet so are the commercial risks, with each new chemical entity (NCE) requiring 10-12 years' development, and only one in seven new, licensed medicines going on to be a commercial success.(2)

Setting the political debate to one side, the sector has made enormous efforts to reduce costs and improve productivity over the past two decades, despite an ever-increasing burden of regulation. Production and packaging models have been streamlined, with strategies such as greater use of outsourcing and make-to-order rather than make-to-stock deployed more frequently for commercially-available products.

Upstream, the management of clinical trials has changed beyond all recognition over the past two decades. Outsourcing is now standard practice, and trials are managed by an extensive, expert community of CROs – currently growing at around 10% per annum – and a network of associated service providers. And, more recently, the geography of the clinical trials map has changed beyond all recognition as traditional centres for studies are replaced by new hotspots in emerging markets such as China, India, South Africa, Latin America and Eastern Europe.

This strategy reflects the trend for establishing or transferring manufacturing operations to lower-cost economies, and the savings achievable are highly significant. What is also true, however, is that management of studies has become much more complex as a result.

Clinical trial protocol development may begin in one country, with review performed by members in corporate locations in another two countries, study execution managed by three corporate locations and two outsourced partners … and so the trail continues. The number of study sites in emerging markets will continue to increase for the foreseeable future as pharmaceutical and biotech companies seek to contain the costs of drug development.

While significant, cost reduction is not the sole reason for conducting studies in emerging markets. Patient recruitment has proven to be a major obstacle in recent years, with as many as 80% of trials failing to recruit on time. With speed to market paramount for any new pharmaceutical product, the knock-on effect of delays at the study stage should not be underestimated. Population profiles (urban/rural) in emerging markets favour easier recruitment of study subjects than in developed markets, aided by the fact that the range and degree of diseases is generally greater. Additionally, patients are more likely to be drug- or treatment-naïve, which contributes to clearer trial indicators. Many of the developing nations have excellent Information Technology (IT) and Intellectual Property (IP) infrastructures in place to support local study sites.

Yet alongside the many benefits of this model, there are a number of geographical and cultural pitfalls that, if not anticipated and planned for, have the potential to negate some or all of the advantages gained from employing study sites in emerging markets. Time zone and language variations, together with complex and differing import licence requirements, are some of the general issues to be considered. Pharma is a global industry open for business 24/7, so delays due to regional time differences are simply untenable.

More specific logistical problems can arise where the study sponsor does not have its own operation in the territories where trials are conducted – set-up and management without local resources can be particularly challenging.

It is in scenarios such as this that the contract sector is the ideal solution: many of the leading global CROs have established their own operations in emerging markets or developed in-region partnerships.

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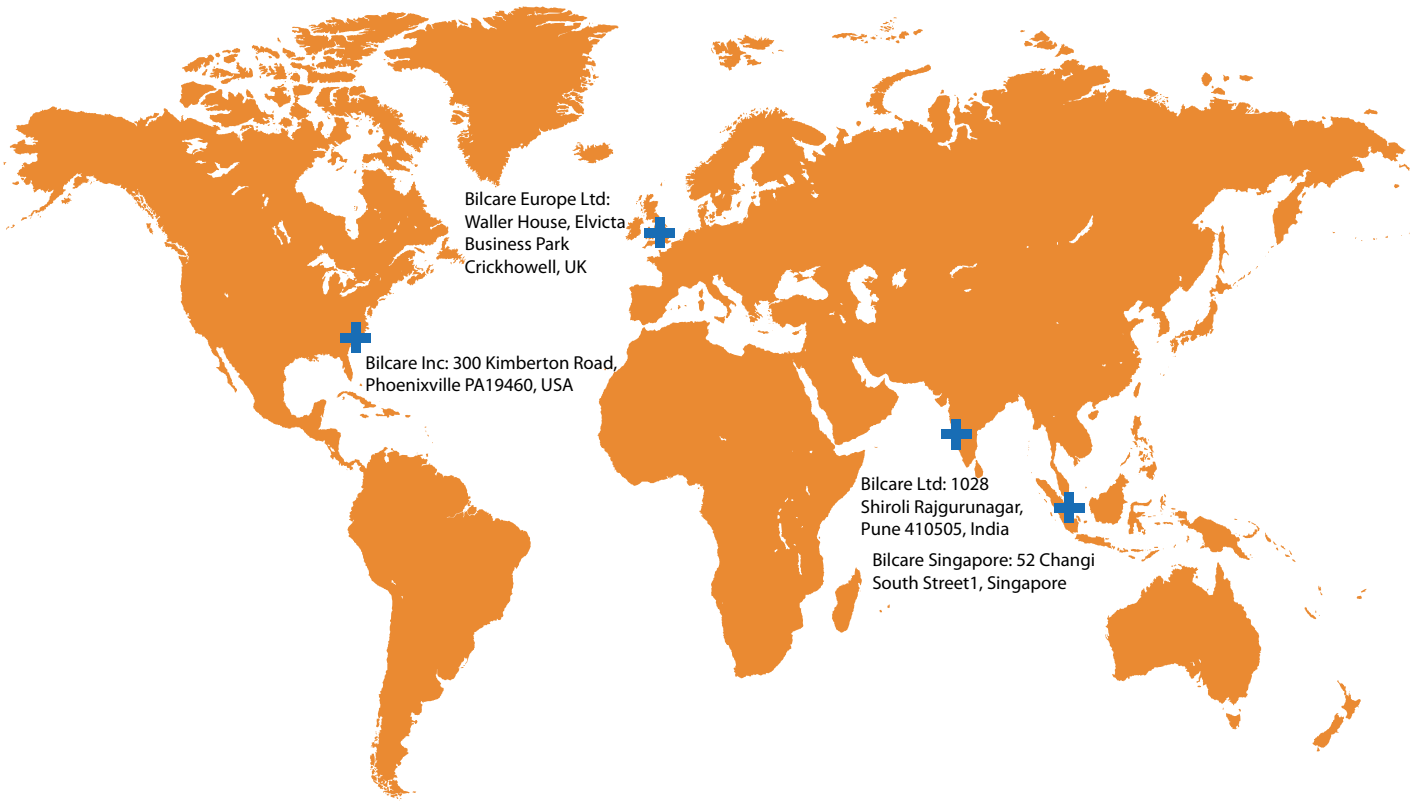

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Equally important is for the CRO community to be able to call on highly-qualified service suppliers to fulfil trial requirements. Where the manufacture and supply of commercially-available pharmaceutical products is concerned, it is now the norm for packaging to be carried out at a regional or local level. However, the smaller volumes of product involved in clinical trials dictates centralised production, meaning that service companies must have expertise in supplying to many markets globally, depending on the scale of the trial.

The vast and growing counterfeit trade affecting commercially-available pharmaceutical products is less of a concern for clinical studies, but nevertheless, there is a perception that much of this trade originates in emerging markets, which CROs may wish to address in managing studies. An experienced service provider will be able to offer reassurance in the form of validated test certificates for all product released for clinical trials, tamper-evident closures, and options for track-and-trace. The use of compliance-enhancing packaging, which is generally more expensive and complex and therefore less attractive for counterfeiters, is a further possibility, as is auditing the supply chain to identify and eliminate or strengthen any weak links. Operating on a Just-In-Time basis minimises the amount of product in transit and reduces risk still further. Dating regimes are another potential issue where studies in emerging markets are concerned, since some regions do not have the expiry date as standard as part of their labelling regime. Where this is the case and it is not practical to return clinical supplies to the original supplier, a packaging services provider would need to co-ordinate in-region application or updating of expiry dates by issuing approved depots with appropriate labels and instructions; overseeing collection and deliveries of packs to be dated and generating an audit trail by means of completed documentation and photographs of the updated packs. It is not a particularly high-tech solution but it is one that works, and which demonstrates the flexible approach required when working in emerging markets.

All this is, of course, in addition to the plethora of highly-specialised services these companies need to offer for the clinical trials market: pack design and comparator sourcing, a wide variety of packaging technologies, such as blistering, bottling, pouching, carding, walleting, and over-encapsulation. Multi-site studies often dictate complex labelling requirements, including patient information in multiple languages, randomisation and code breaks. Expert regulatory support and QP release into different markets and regions, an intimate knowledge of import/export regulations for different countries, cold chain, controlled drug and shipping capabilities par excellence are further requirements, along with returns management and the ability to interface with a range of IVRS systems for smooth and successful trial implementation.

Companies that can deliver all these services and capabilities are highly-valued by CROs and are increasingly involved at tender stage to demonstrate the availability of a 'one-stop shop'. For example, by working with an in-region service provider with the right credentials, a non-European-based CRO (or, indeed, study sponsor) managing a trial involving sites in various Eastern European markets, can access all the regulatory support required for almost 30 countries via a single source – a huge benefit in terms of streamlining operations. Further, with many emerging markets conscious of the need to validate their credentials by placing patient safety firmly at the top of the agenda, keeping abreast of legislation updates is a challenge in itself and one best left to the experts.

This complex remit is way beyond the capabilities of smaller organisations, so it is no surprise that where contract packaging was once a very local activity, this sector too is looking to globalisation as the way forward. Brecon Pharmaceuticals is no exception: acquired in 2006 by AmerisourceBergen Corporation, one of the world's largest pharmaceutical services companies with a focus on the pharmaceutical supply chain, we have now established identical capabilities either side of the Atlantic to ensure a completely harmonised service for the delivery of clinical trials supplies, encompassing packaging, storage & distribution and a returns management solution for clinical trials clients. Uniform procedures and paperwork ensure a seamless client interface, regardless of which site is taking the lead and providing the service.

However extensive the technical and intellectual capabilities of a service provider, in a global business, the need for 24/7 communication and information remains paramount. Where clinical studies across multiple territories are involved, a project manager may wish to check on inventory, shipping schedules, location of supplies in transit or other aspects of his study at any given moment: waiting for a supplier to come online simply is not acceptable when business days may well be eight or more hours apart. A robust IT infrastructure is key, with a platform able to deliver the flexibility to accommodate varying client requirements, while delivering the high levels of control required for clinical trials in particular. A major investment at Brecon will see all these objectives achieved via a single platform later this year, when we combine and migrate various information onto a single ERP system. Rolling out across the AmerisourceBergen Packaging Group, the system will offer a dedicated web portal for each client, which can be customised to provide real-time status information according to a range of client-specified criteria, thereby facilitating the delivery of a complete service encompassing packaging services, technical and regulatory expertise and complete transparency for clients, around the clock and around the globe. ■

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1 So That's Why It's So Expensive, Business Week, August 14, 2006.
2 Association of the British Pharmaceutical Industry.

Steve Kemp has 15 years' experience of pharmaceutical packaging. He is Business Development Director at Brecon Pharmaceuticals, a post he has held since joining the company in 2001. Prior to joining Brecon, he was Commercial Services Director at PCI/Unipack, subsequently Cardinal Health. Since 2008, Mr Kemp has served as Vice-Chairman of the European Healthcare Compliance Packaging Council (www.hcpc-europe.org), whose mission is to assist and educate the healthcare sector in the improvement of patient compliance through the use of packaging solutions.
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News

PAREXEL OPENS NEW PATIENT RECRUITMENT SUPER SITE FOCUSED ON ACCLERATING EARLY PHASE DEVELOPMENT

PAREXEL International, a leading global biopharmaceutical services provider, has expanded its early phase drug development capabilities to provide biopharmaceutical companies with improved access to accelerated development through the opening of a new patient recruitment Super Site in Port Elizabeth, South Africa. This early phase unit in South Africa serves as one of PAREXEL's Super Sites, located worldwide, which provide high enrollment potential for clinical studies. These Super Sites draw on dedicated patient recruitment specialists and relationships with local health care professionals as well as call center and database capabilities to allow for a high number of patients to be recruited in a rapid timeframe.

As part of the official inauguration of its early phase unit in Port Elizabeth, South Africa, PAREXEL will bring together leading experts from around the world for an invitation-only symposium on February 24, 2010 entitled "Early Drug Development: The Challenge to Get Better Data Sooner." The symposium will address the latest trends and best practices to assist biopharmaceutical companies in overcoming key early phase development challenges.

Members of PAREXEL's dedicated team of early phase experts, who have in-depth scientific, therapeutic, and regulatory expertise, will be in attendance at the event to discuss the design and implementation of First-in-Human through Proof of Concept studies for new drug entities across a broad range of therapeutic indications. These experts will address how biopharmaceutical companies can avoid costly late stage clinical development failures by making better and faster go/no-go decisions.

With locations across three continents, PAREXEL's other early phase units are located in Baltimore, Maryland and Los Angeles in the United States; London, United Kingdom; Berlin, Germany; and Bloemfontein and George, South Africa. PAREXEL's early phase units provide rapid study-start up and unrivalled direct access to diverse patient populations as well as healthy volunteers.

For more information about PAREXEL's early phase development capabilities, visit: http://www.PAREXEL.com/early_phase.html.

BIOCAIR HAVE NEW OFFICES IN CHINA

Biocair have expanded their operations into China, with new offices in Shanghai. They are now a 'Wholly Foreign Owned Enterprise' with a Chinese business license. The opening ceremony was held on November 12th and was attended by Carma Elliott, the British Consul General in Shanghai.

Biocair was established in 1987 and is a proven international specialist in transporting temperature sensitive biological materials and drugs for clinical trials in and out of the main pharmaceutical and biopharmaceutical clusters in UK, Europe, USA and Asia.

Managing Director, Andy King commented "This expansion into China is a key step in our international business development plan in response to a growing customer a demand in the region". He went on to say, "We really appreciated all the encouragement and support we have had from customers, which helped us make this investment decision to enter the market in China."

For more information visit: www.biocair.com

"PharmaVigilant Integrates Imaging Functionality Into I-Vault 2.3 Product Release"

With an increase in the use of medical imaging in clinical trials, sponsors have expressed a need for incorporating an integrated imaging capability into their trial technologies. To meet this growing need, PharmaVigilant, a clinical trial technology provider, has integrated imaging functionality into the new release of its clinical trial technology suite, I-Vault 2.3. This updated solution allows sponsors to store, retrieve and review clinical data and MRI images through a consolidated solution, leading to increased transparency and efficiencies and significant cost savings.

For further information please visit www.pharmavigilant.com.

SFDA Issues Good Manufacturing Practice (GMP) for Medical Devices

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.

Source: Asia Medical eNewsletter

Clinical trials of the first H1N1 vaccine to be used on Indians from mid-February will started on Wednesday 20th of January 2010.

Three medical institutes in Delhi, Chandigarh and Pune will test the H1N1 vaccine made by French vaccine manufacturer Sanofi Pasteur in a three-week bridging study on 100 Indians. The Indian Council of Medical Research (ICMR) wants to be sure that the vaccine, tried and tested in foreign countries, is safe for use on the Indian population.
India is importing 1.5 million doses of this single-shot vaccine by February 15 for use on frontline healthcare workers.
Drug Controller General of India Dr Surinder Singh said even if the vaccine passed the three-week test for safety and efficacy, those who receive the shot during trials would be followed for six weeks to see if they report any serious side effects like the Guillain-Barri Syndrome (GBS) -- a rare disease in which the body damages its own nerve cells, causing muscle weakness and sometimes paralysis.
Meanwhile, India's indigenous H1N1 vaccine is expected to be available by April 15 and could cost between Rs 80-Rs 100.
Cadila Healthcare on January 3 started human trials of India's live and inactivated indigenous H1N1 vaccine on 200 subjects.
Three other Indian companies -- Serum Institute (Pune), Bharat Biotech International (Hyderabad) and Panacea Biotec (New Delhi) have also been given clearance by the DCGI to conduct human trials, which are expected to start soon.
While Serum will test its vaccine on around 350 people, Panacea has a subject size of over 1,100 and Bharat of 160.
Dr Singh said, "If all goes well with the Indian vaccines and they prove safe and effective, they should be available commercially between April 15-30. India's vaccine manufacturing market is very matured. Around 60 % of all vaccines in the DTP family are produced and supplied globally by Indian companies. 90 % of the measles vaccines are manufactured by India. India's H1N1 vaccine should be very good."
Experts say no vaccine is 100 % safe for everyone. People with allergies to eggs, for example, can't take flu vaccines because eggs are involved in the manufacturing process. H1N1 has spread to 210 countries. In India, it has infected over 28,300 people and killed 1,141.
"Usually, a vaccine test takes years. But since this was a pandemic virus and we needed a vaccine urgently, the Indian companies were given permission for Phase 1 to Phase 3 trials at one go to cut down on time," Dr Singh said. **NEW DELHI: 20th Jan 2010**

CRITERIUM, Inc., Global CRO, expands staff in 3 countries for 2010

(January 29th, 2010 – Saratoga Springs, NY)
Criterium, Inc., a full-service CRO is pleased to announce expansion of their staff in 3 countries – the USA, India and South Africa. The expansion is part of their 2010 business plan to increase the ability to service clients, accommodate current sponsors and project deliverables, and conduct trials in a wider range of local and regional areas around the globe. The new staff is being added to their monitoring services, business development and regulatory departments. This will allow Criterium to provide more customized monitoring services, increase business development around the globe, and provide proven regulatory assistance to sponsors who need in-country services. "We think of ourselves as an 'agile' company, with a 'green' focus – we keep our services well-planned and competitive, and we add staff prudently to ensure top quality work and people on all studies we do," said John Hudak, president and founder. Director of Global Affairs, Dr. Lawrence Reiter also added: "Scientific ventures drive the economy, not the other way around, so we look at 2010 with a predictive optimism. Adding staff will allow us to do more for our clients this year."

Contact: Claire Wynters, Public Relations & Media (518) 583-0095 crwynters@criteriuminc.com

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