

JOURNAL FOR CLINICAL STUDIES



July 2009

Your Resource for Multisite Studies & Emerging Markets

Therapeutic Cancer Vaccines

And the Need for Innovative
Approaches

Powerful Web-based LIMS

Supports Clinical Trial
Expansion into Emerging
Countries

Challenges & Options

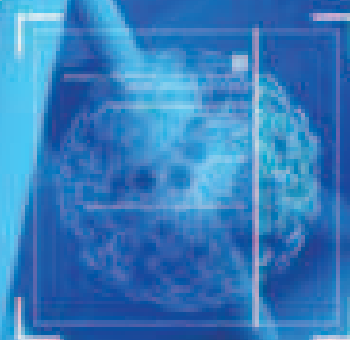
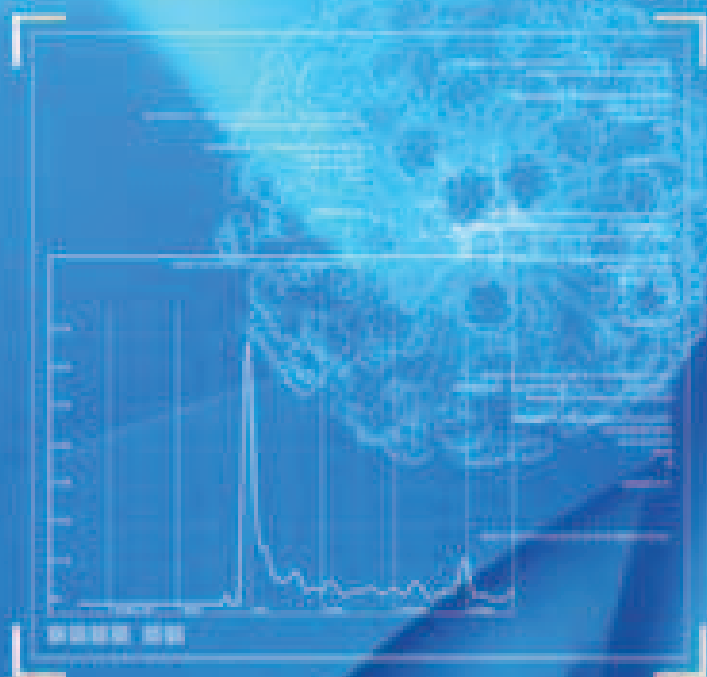
In the conduct of Clinical Trials in
Emerging Countries in Africa and
the Caribbean

Vaccines

Preventive and therapeutic
vaccines and adjuvants on
the rise.

www.jforcs.com

YOUR LOGICAL CHOICE IN CLINICAL OUTSOURCING
TO RUSSIA AND UKRAINE



CROMOS PHARMA

- HIGHEST RECRUITMENT AND RETENTION RATES
- LARGE POOL OF DRUG-NAIVE PATIENTS
- SPECIALIZED DISEASE-SPECIFIC MEDICAL CENTERS
- FAST REGULATORY APPROVALS

UKRAINE: MYCHALOVSKAYA STR 18-B, OFFICE 804, KYIV, 01001, TEL: +38 044 378 81 88, FAX: +38 044 378 81 88, E-MAIL: INQUIRY@CROMOSPHARMA.COM
USA: 1500 SW PARK AVENUE, SUITE 100, PORTLAND, OR 97201, TEL: +1 360 431 38 18, FAX: +1 360 394 98 47, E-MAIL: INQUIRY@CROMOSPHARMA.COM
RUSSIA: KRAYCHENKO STREET 18-04, 119 337, MOSCOW, TEL: +7 495 594 91 72, FAX: +7 495 478 55 43, E-MAIL: INQUIRY@CROMOSPHARMA.COM

WWW.CROMOSPHARMA.COM

KEYNOTE ADVISOR

Steve Heath

MANAGING DIRECTOR

Martin Wright

PUBLISHER

Mark Barker

MANAGING EDITOR

Jake Tong

EDITORIAL COORDINATOR

Janet Douglas

EDITORIAL ASSISTANTS

Nick Love, Kevin Cross, Lanny McEnzie

DESIGN DIRECTOR

Anika Mistry

RESEARCH & CIRCULATION MANAGER

Dorothy Brooks

ADVERTISING SALES

Victoria Winward, Zareen Monet

ADMINISTRATOR

Barbara Lasco

FRONT COVER

Inhouse - Design

PUBLISHED BY:

Pharma Publications

www.jforcs.com

Address: Building K Unit 104

Tower Bridge Business Complex

Tower Point

London

SE16 4DG

Tel: 0044(0)2072375685, Fax: 0044(0)2073947415

Email all correspondence to: info@pharmapubs.com

Journal for Clinical Studies – ISSN 1758-5678 is published bi – monthly by PHARMAPUBS.



The opinions and views expressed by the authors in this journal are not necessarily those of the Publisher, the Consultant Editor and the companies named herein are not responsible for such opinions and views, or any other inaccuracies in the articles. The entire content of this publication is protected by copyright. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form, by any means – electronic, mechanical, photocopying or otherwise – without the prior permission of the Publisher.

2009 PHARMA PUBLICATIONS

Contents

6 EDITORIAL ADVISORY KEYNOTE

WATCH PAGES

8 FDA Watch

- Tobacco regulation - President Obama signs bill regulating tobacco
- Drug Side Effects
- Rejected Drugs - Groups urge FDA to release info on rejected drugs
- Enforcement - U.S. marshals seize drug products manufactured by Caraco Pharmaceutical Laboratories

By: Joseph Pickett of Expertbriefings.com

10 Current Good Manufacturing Practice for Phase 1 Clinical Trial Products

The US Food and Drug Administration (FDA) announced a final rule last July regarding the current good manufacturing practice (CGMP) regulations for human drugs, including biological products, to exempt most phase 1 investigational drugs from complying with the CGMP requirements. This amendment took effect September 15, 2008.1

By: Deborah A. Komlos, Thomson Reuters

12 Australasia Watch

This month in Australasia watch we move our thoughts from Australia to New Zealand. New Zealand offers healthcare companies a pragmatic regulatory/ethics process and a rapid start for clinical trials. Drug and biotech studies are submitted to Medsafe in parallel with the ethics application and take two to four weeks to approve, and can start subject to ethics approval. New Zealand continues to be attractive centres of research excellence in early phase product development and beyond.

By: Russell Neal & Gerard Dunne of Clinical Research Network (CNS Pty. Ltd.)

14 Caribbean Watch

The plan to explore the Caribbean as an emerging market to conduct clinical research has included contacting the appropriate country officials including the Ministry of Health, Chief Medical Officer and discussing the interest in conducting clinical trials in their country. The plan also included obtaining any recommendations, requirements and past and current experiences as well as establishing a working knowledge of the process and procedures for obtaining local Ethics Committee approval.

By: Francine Hakim of Caribbean Clinical Research Associate.

16 China Watch - Drug Development in China —Relative Regulations on International Multicentre Trails

With more and more attention to performing international multicentre trails in China, SFDA laid down some regulations for international multicentre trails in Provisions for Drug Registration. Firstly, applications on performing international multicentre trails in China should also follow the drug classification. The applications should be presented according to the requirements of the registration application of imported drugs; the time needed from application to approval is about 6-8 months.

By: Dr. Xunting Zeng of INCROM CHINA

18 CLINICAL TRIALS REGULATORY PROCESS IN INDIA

CDSCO (Central Drug Standard Control Organization) is the central authority headed by DCGI (Drug Controller General of India) responsible for the clinical research regulation in India. Kamal Shahani of Cliniminds India explains the key regulations and guidelines which govern the clinical trial regulation in India



Contents

20 Checklist for GMP issues at CROs:

CROs being well familiar with GCPs sometimes lack in GMPs as regards standardized procedures for receipt, storage, handling, dispensing and return of study medication as well as qualification of storage units, deviation procedures and documentation. The check list below may support CROs covering GMP related issues.

By: Dr. Claudio Lorck of Temmler AG.

REGULATORY

22 What is the line between CRO and sponsor responsibilities, and the difference between the delegation of the tasks and delegation of the responsibilities?

Possible contents:

With medicine development timescales taking approximately 10 to 12 years from discovery to market release. And complicated systems and deeply involved procedures, the costs of development of new medicines are rapidly increasing and the role of R&D and CRO organisations becomes critical. Sule Mene of Mene Clinical Research asks - What is the line between CRO and sponsor responsibilities, and the difference between the delegation of tasks and responsibilities?

MARKET ANALYSIS

28 East and West – Clinical Trials in the CEE

With 15 % annual growth predicted in the CRO industry in Eastern Europe (CEE) between 2008 and 2012, the region has positioned itself as an attractive region for performing clinical research, and has become a high-quality and cost-effective option for companies with drugs in development. Of course, with more than 20 countries, it is unrealistic to describe to CEE in general terms, but there are common elements that make these countries attractive. Janos Filakovszky of Quintiles explains the current conditions of the entire market.

32 CHALLENGES & OPTIONS IN THE CONDUCT OF CLINICAL TRIALS IN EMERGING COUNTRIES IN AFRICA AND THE CARIBBEAN

There have been recent efforts to conduct clinical trials and training in several countries in Africa and the Caribbean. The required standards for conducting research on new drugs are not always able to be met in both developing and emerging nations. Additional factors that must be taken into consideration when implementing clinical trials and training in these countries are: lack of facilities, government policy interference, non-indigenisation policy, poverty, ignorance, diseases, corruption, communication problems, insufficient and inexperienced personnel to name a few. Gbolahan Fatuga of Calegio Clinical One Vision goes on to examine each of these and their effect(s) on the conduct of a clinical trial.

THERAPUTIC STUDIES

36 Therapeutic Cancer Vaccines and the Need for Innovative Approaches

A new generation of targeted therapeutics for the treatment of cancer is emerging from the growing knowledge base of biomedical drug discovery. Based on a biological approach, novel cancer therapeutics currently under development include agents in the areas of vascular targeting, antisense, gene transfer, immunotherapies, and apoptotic induction. Jennifer R. Weidman, PhD, RAC of Cancer Advances Inc explains why these innovative treatments hold the promise of improved therapeutic choices for selected cancer patient populations and have the benefit of diminished side effects compared with traditional cytotoxic therapies.

40 Vaccines: preventive and therapeutic vaccines and adjuvants on the rise

There remain major areas of unmet medical need which could be addressed by further research and development into preventive and therapeutic vaccines. Additionally, there are seemingly never ending challenges for vaccine

OPVERDI

The Electronic Data Capture System

FOR MORE THAN 10 YEARS

A tool from the Experts for the Experts.

Modern technology continues to play an increasingly important role in how we do business. The more complex and sophisticated new product development is, and the tighter the time constraints fuelled by international competition are, the greater the impact modern IT tools have on your study. An increase in the efficiency and quality of various phases of a trial equals earlier market entry.



OPVERDI

an online web based client-server system for electronic data capture which allows unique interactive assistance between users of data entry.

OPVERDI

was developed especially for clinical research by an interdisciplinary group of experts with many years of experience in international clinical research

OPVERDI

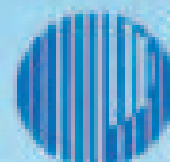
is an established EDC system which can not only store data entered in the classical way, but also import and process data generated by an expanding selection of mobile telemedical devices.

Dr. Oestreich + partner
Research and Marketing in Medicine and Pharmacy GmbH

Hensering 102-104
50670 Cologne, Germany

Phone: +49 (+221) 9128710
Fax: +49 (+221) 9128711

E-mail: OPInfo@OandP-CRO.com
Web Site: www.OandP-CRO.com



Founded 1991

Contents



manufacturers to overcome emerging and re-emerging infectious diseases with preventive vaccines. There is also strong demand for the development of therapeutic vaccines in patients with autoimmune and allergy-based disease, linked to high tumour incidences and growing evidence of resistance to standard chemotherapy regimes. Ralf D Hess, PhD, Principal Consultant, PAREXEL Consulting & Partha Ghosh, MD, Director, PAREXEL Consulting evaluates why, reaching these goals may require new and improved adjuvants for the development of more effective and more powerful vaccines especially in immunocompromised populations.

45 Malaria Vaccine Candidates- an overview

Since the epidemiology of malaria varies enormously across the globe, it may be necessary to adopt different vaccine development strategies to target the different populations. Looking at the malaria parasite life-cycle, we can see that there are various areas that can potentially be targeted by vaccines. The most recent advances in the field of sub-unit vaccine development include the use of DNA vaccines. Dr Sheperd Moyo of OnQ Research PTY LTD gives us an overview of the main vaccine candidates that have managed to undergo human testing.

49 Diagnosis of Brucellosis at the present stage & Pathogenesis grounds of immunity-modulated therapy of brucellosis

One of the main conditions of successful treatment in any disease is its correct and timely diagnostics. Early diagnostics in brucellosis has the great epidemiological value and allows to carry out antiepidemiological actions in the seat of infections timely. Sh. A. Kulzhanova of Semipalatinsk state medical academy, Semey city, Kazakhstan, discusses the role of numerous immunological breaks for each concrete brucellosis patient and to approach with validity the treatment of a given illness, i.e. differential application of non-specific immunity-modulated therapy with the influence on the concrete chains of immunity.

LABS & LOGISTICS

52 Fundamental errors when working with central laboratories

Central laboratory services are complex especially due to the logistical tasks involved. Bad understanding of processes during the planning phase has the irrevocable consequence that sites may prepare their samples inappropriately, that samples may undergo unexpected delays during shipment and that lab results may not be available at the site for the next patient's visit. Dr. Hermann Schulz of Interlab GmbH suggests how Sponsor companies (essentially Pharma and Biotech) can do better during the selection process.

56 Powerful Web-based LIMS Supports Clinical Trial Expansion into Emerging Countries

Recruitment of subjects is a major bottleneck in many clinical studies causing problems to companies seeking regulatory approval for new products. However, with large populations eligible to participate in clinical studies, an ample supply of trained clinical investigators, and the opportunity to reduce trial costs by up to half compared to the U.S. or Western Europe, clinical trial activity is on the rise in many emerging markets including Eastern Europe, Latin America, Asia, and Africa. Successful execution of a clinical trial in these emerging countries requires that the clinical trial specimen collection, handling, shipping, and testing processes are tightly managed despite these challenges. A flexible and feature rich Laboratory Information Management System (LIMS) can accommodate new investigator and specimen testing sites and will enable effective management of the kit supply chain, specimen collection, storage, testing, and laboratory result management. *By Tamar.Harris & Ed Krasovec of Starlims*



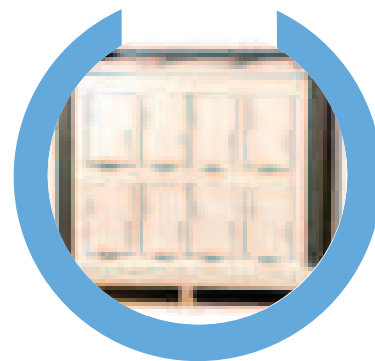
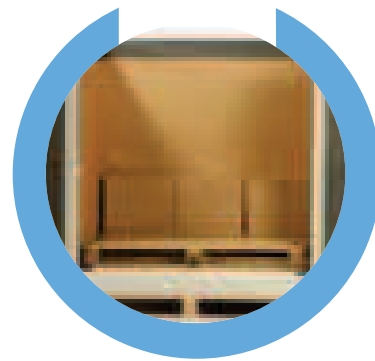


Chilltherm® Global CTG1130 - Temperature controlled packaging for bulk shipments

The Chilltherm® Global CTG1130 from Laminar Medica is designed to protect bulk shipments of temperature sensitive goods in transit. The Chilltherm® CTG1130 has been designed to accommodate a full pallet of product.

The Chilltherm® Global CTG1130 is delivered flat-packed for ease of transportation and storage. The system can then be assembled and loaded quickly and easily during quieter periods and placed in a cold room until needed, improving the efficiency of your operation.

- Qualified to maintain +2°C - +8°C for 96 hours
- Supplied flat packed for easy storage
- Simple and fast to assemble; step by step assembly guide available
- Option to part-assemble in advance
- Good fit on an airline skid



Tring

United Kingdom

+44 (0) 1442 828664

enquiries@laminarmedica.co.uk

www.laminarmedica.com



Distributors

North America

Saf-T-Pak Inc.

+1 410-553-6066

sales@saftpak.com

www.saftpak.com



Vodnany

Czech Republic

+420 38 331 0000

enquiries@laminarmedica.cz

www.laminarmedica.cz



Canada

Saf-T-Pak Inc.

+1 780-486-0211

sales@saftpak.com

www.saftpak.com



laminarmedica
insulated shipping systems



Singapore

Aeris Dynamics

+65 6296 8368

sales@aeris.com.sg

www.aeris.com.sg



Editorial Advisory Keynote



By Steve Heath, Head of EMEA - Medidata Solutions Inc.

In the May edition of JfCS, Parexel's Mark Goldberg looked forward to the DIA to be held in San Diego in June. Having just returned from this event, I was left with the impression of an industry still passionately engaged in trying to fulfil its mission of developing "better medicines" and improving patient safety. Conference attendee numbers seemed somewhat down

on last year; the prevailing economic climate which has severely impacted travel budgets in many companies, together with concerns around H1N1, combined to reduce both US domestic and international (non-US) participation at DIA. The exhibition hall was also quieter than normal but happily many of the sessions were full and engaged with lively debate. As ever, DIA members continue to give of their time and expertise and their passion for improvement.

The impact of technology on clinical development together with the associated process enhancements needed to take advantage of these technologies continues to be a positive theme. Technologies such as EDC are now being seen by many large organisations as a given in more and more trial situations. There is a greater level of confidence that the major players in the EDC space, including the CRO community, can effectively conduct multi-country, multi-language trials using large and diverse patient populations, and that the data resulting from these studies can be made available for analysis in timelines meaningful for sponsor and regulator - and all of this while helping facilitate rapid reporting of safety-related data.

This potentiation of global trial capability via technology plays into the need for access to broader patient populations in geographies such as the BRIC countries, Latin America and SE Asia. Also, as political and social demand for development of enhanced treatments for infectious diseases increases, conducting "more studies - more effectively" in areas that have been somewhat neglected historically, including sub-Saharan Africa, will demand that technology and service providers ensure that useful tools are available to aid clinical researchers.

Global Pharma is under pressure from all sides: society, politicians, shareholders and regulators all have expectations and demands of the industry which have to be meaningfully reconciled. A key economic requirement is to improve development efficiency. Cost containment at the governmental/insurance payor level combined with the need for maintenance of shareholder value mean clinical development simply has to follow the lead of its cousins in Pharma manufacturing and sales supply, and take advantage of technology and process optimisation opportunities. While there are uncertainties around the detail of the Obama administration's

healthcare reform process, Global Pharma needs to be in a more efficient state to be able to react to any stimulus opportunities presented, as well as to any negative impacts that the highly visible drugs bill component of healthcare cost will deliver.

An important element of this is the development of meaningful standards to ensure interoperability within data flows and technologies. At the San Diego DIA, one of the busiest exhibition stands appeared to be the CDISC (Clinical Data Interchanged Standards Consortium), which has been one of the major forcing elements in our industry in the drive towards standards.

Suppliers and sponsors alike should ideally be able to function within a mutually agreed standards universe. At DIA this manifested itself in dialogue in several sessions about whether so called integrated suites of technology, or best of breed technologies, linked by emerging open standards such as CDISC ODM/STDM or Web Services was the better choice. The possible technical and process constraints of the former model vs. the potential for greater commercial complexity of the latter seem to be two main areas of the debate.

Technology can and is driving better downstream decision-making; more rapid access to information can facilitate "fail fast fail early" approaches. Adaptive trial and other innovative trial conduct methodologies, which have yet to achieve the overall breakthrough level hoped for a little while ago, are also driven by rapid access to technology such as interactive randomisation and EDC.

Looking upstream, interesting work based on standards-driven global libraries of forms and functions has already taken place to ensure more rapid development of deployable studies. The next level of (cost and time) efficiency gains in this area will likely come from enhancement of the analysis of prior studies as a feed into the next process step. For example, being able to analyse the effectiveness of data collected for frequency of usage and end point validity and potentially benchmarking this against industry or therapeutic area peers could allow for significantly enhanced decision-making. Clinical protocol optimisation based on appropriate open technologies could facilitate faster recruitment, perhaps involving fewer patients, as well as lay a foundation for standards-driven data streams to other technology systems in the development process, such as site supply management. The aim is to drive cost, complexity and time out of clinical development and help make "better medicines" available sooner to more people.

A final thought: as the industry moves towards greater operational efficiency the interplay between sponsors, service and technology providers, and indeed the regulators, is becoming more complex and therefore has to rapidly mature. Enhancement of trust and openness in dialogue need not damage commercial confidentiality. The drive to demonstrable value in all aspects of clinical development will require the industry as a whole to mature to take advantage of the opportunities that await us.

Editorial Advisory Board

Art Gertel, VP, Clinical Services, Regulatory & Medical writing, Beardsworth Consulting Group Inc.

Bakhty Sarymsakova - Head of Department of International Cooperation, National Research Center of MCH, Astana, Kazakhstan

Catherine Lund, Vice Chairman, OnQ Consulting

Chris Tierney, Business Development Manager, EMEA Business Development, DHL Exel Supply Chain, DHL Global

Chris Tait, Life Science Account Manager, CHUBB Insurance Company of Europe

Devrim Dogan-Guner, Medical Director, ENCORIUM

Elizabeth Moench, President and CEO of Medici Global

Francis Crawley, Executive Director of the Good Clinical Practice Alliance - Europe (GCPA) and a World Health Organization (WHO) Expert in ethics

Georg Mathis Founder and Managing Director Appletree

Ghassan Ahmed, Vice President, Medical & Regulatory Affairs, ClinArt International

Heinrich Klech, Professor of Medicine, CEO and Executive Vice President, Vienna School of Clinical Research

Hermann Schulz, MD, CEO, INTERLAB central lab services - worldwide GmbH

Janet Jones, Senior Director, Strategic Patient Access, KENDLE

Jerry Boxall, Managing Director, ACM Pivotal.

Jeffrey W. Sherman, Chief Medical Officer and Senior Vice President, IDM Pharma. Board Member of the Drug Information Association.

Kamal Shahani, Managing Director of Cliniminds - Unit of Teneth Health Edutech Pvt. Ltd.

Karl M Eckl, Co-founder, Executive and Medical Director, InnoPhaR Innovative Pharma Research Eastern Europe GmbH

Mark Boulton, Healthcare Market Sector Leader, DNV

Mark Goldberg, Chief Operating Officer, PAREXEL International Corporation

Maha Al-Farhan, Vice President, ClinArt International, Chair of the GCC Chapter of the ACRP

Nermeen Varawala, Vice President, Scientific & Medical Affairs, PRA International

Peggy A. Farley, President and Chief Executive Officer of Ascent Capital Management Inc.

Rob Nichols, Director of Commercial Development, PHASE Forward

Stanley Tam, General Manager, Eurofins MEDINET (Singapore, Shanghai)

Stefan Astrom, Founder and CEO of Astrom Clinical Research

Steve Heath, Head of EMEA - Medidata Solutions, Inc

T S Jaishankar, Managing Director, QUEST Life Sciences

HELLO

I am Karl M. Eckl,

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

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

Why are these studies so difficult to perform?

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

I set up INNOPHAR to provide you with:

- Patient populations which are the most critical ones to recruit for phase I and IIa studies (e.g. renal or hepatic impaired or oncology patients)
- High quality services of our own clinical sites specifically tailored for these types of clinical studies
- The service directly and not through any sub contractor
- Own patient panels, we perform these studies frequently
- Expertise, as phase I and IIa studies in these types of patients are our core business
- We recruit patients in huge polyclinics which cover patient data from 50,000 patients or more each. We co-operate with 5 – 10 polyclinics, and as a result we can give exact time windows for recruitment, which is a rare thing in this business.

**Our Formula for success can be yours.
Just contact me or my colleagues at:**

INNOPHAR GmbH
Innovative Pharma Research
Eggersberg 4A. D-94375 Stallwang. Germany

Tel: +49 (0) 9964 6010216
Fax: +49 (0) 9964 6010217

E-Mail: contact@ipr-ee.com
www.ipr-ee.com

Our expertise lies in:

Cardiovascular
CNS (including psychiatry)
Endocrinology
Infection disease
Asthma and pulmonology
Oncology
Liver disease (alcohol and toxic cirrhosis and hepatitis B and C)
Kidney disease (nephrology and urology)
Gastroenterology
Postmenopausal women
Elderly population
Gynaecology
Rheumatoide arthritis
Male and female healthy subjects
Haematology
Ophtalmology
Pain patients
Surgery and neurosurgery



Dr. Karl M. Eckl
Managing Director
INNOPHAR GmbH



FDA watch

Tobacco regulation

President Obama signs bill regulating tobacco

President Obama signed legislation on June 23 that will give the US Federal Government broad new power to regulate the manufacturing, advertising and marketing of cigarettes and other tobacco products, The Washington Post reported on June 24.

Obama signed the bill into law during a Rose Garden ceremony, where he hailed it as a landmark measure that would help rein in some of the health damage caused by smoking, which is responsible for more than 400,000 deaths in the United States each year. One-fifth of children in the country are estimated to smoke by the time they graduate from high school.

Obama invoked his own struggles to quit smoking as he pointed out that almost 90 per cent of smokers begin the habit by the time they turn 18. "I know - I was one of these teenagers," said Obama, who has frequently talked publicly about his battle, "and so I know how difficult it can be to break this habit when it's been with you for a long time."

The law requires sterner health warnings on cigarette packs, and it may bring about changes in the formulations of cigarettes and cigars.

It will also require manufacturers to disclose the ingredients in cigarettes and other tobacco products and will institute severe limitations on how they are advertised and promoted.

For more information, please visit www.washingtonpost.com.

Drug Side-Effects

Johnson & Johnson's Tylenol should be given in lower doses and the Extra Strength version should be sold by prescription only to curb the risk of liver damage from the 50-year-old painkiller, a US advisory panel said, according to Bloomberg.com.

Outside advisers to the Food and Drug Administration voted 21-16 on June 30 that people should take less than 4,000 milligrams of Tylenol or other over-the-counter products containing acetaminophen in a day. The current maximum equals eight Extra Strength, or 500 milligram, tablets or capsules a day.

The 500 milligram tablets account for more than 90 per cent of US sales of single-ingredient acetaminophen, according to an FDA review of data from IMS Health Inc., and the drug is one of the most widely used medicines in the US. The drug has been a leading cause of liver injury for more than a decade even with efforts to educate users about the danger of taking too much, the FDA says.

"The most important target for our action is unintentional harm, both in adults and in children," said panelist Karl Lorenz, an internal medicine specialist with the Veterans Affairs

Greater Los Angeles Healthcare System. "Education is a weak intervention and we really are looking for more concrete steps."

The panel, meeting outside Washington in Adelphi, Maryland, voted 24-13 to lower the single adult dose to 650 milligrams, or two regular strength tablets, a reduction of 35 per cent. The panel voted 26-11 that the 500 milligram Extra Strength dose should be available through prescription. The FDA may follow the advice of outside panels, although it isn't required to.

For more information, please visit: www.bloomberg.com

Rejected Drugs

Groups urge FDA to release info on rejected drugs

The FDA should make more information available to the public, even on drugs and devices that never make it to the US market, consumer advocates told the health agency on June 25, according to Reuters.

But industry representatives cautioned that findings or data containing confidential company information could harm competition if made widely available.

While the FDA often provides public details on products that win its approval, doctors and consumers could benefit from similar disclosure on those it rejects, several advocates and former FDA staff reviewers said at a public meeting to discuss ways the agency can make its regulatory decisions clearer.

Details on why it declines a new use for a drug already on the market could help protect patients from possible side-effects if doctors are already prescribing it for so-called "off-label" use or as rival drugs are developed, said the Pew Prescription Project's Allan Coukell.

"Lives might have been saved," Coukell, director of the nonpartisan consumer safety group, told the panel of eight top FDA officials.

The FDA, which regulates a wide range of foods, drugs and devices that make up about 25 per cent of the US economy, has ultimate say on whether medications can be sold or whether certain foods must be recalled. It also monitors manufacturing sites and monitors drug risks, among other duties.

But it has come under fire amid a number of scandals involving a variety of products including painkillers, contaminated peppers and peanut butter.

Some critics said the agency, which gets much of its funding from company fees, is too cosy with the industries it regulates.

FDA has adopted a "corporate culture" and focuses too much on company interests instead of science, said Public Citizen Health Research Group Deputy Director Peter Lurie, whose

advocacy group has long challenged many FDA decisions.

Dr. Joshua Sharfstein, deputy commissioner of the FDA and head of the panel, defended the fees earlier this year, saying agency staff make decisions based on evidence.

US lawmakers only recently boosted the FDA's budget.

Industry groups said the FDA could do better at helping consumers understand its actions but warned that too much public detail on products or manufacturing may tip off rivals.

"To provide that type of information before approval would provide competitors with insights ... those types of insights come at a cost, a competitive cost," said Pharmaceutical Research and Manufacturers of America lawyer Jeffrey Francer.

For more information, please visit www.reuters.com

Enforcement

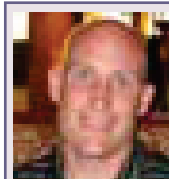
US marshals seize drug products manufactured by Caraco Pharmaceutical Laboratories

US marshals, at the request of the FDA, on June 25 seized drug products manufactured by Caraco Pharmaceutical Laboratories Ltd. (Caraco), at the company's Michigan facilities in Detroit, Farmington Hills, and Wixom. The seizure also includes ingredients held at these same facilities. "The FDA is committed to taking enforcement action against firms that do not manufacture drugs in accordance with our good manufacturing practice requirements," said Janet Woodcock, M.D., director of the FDA's Center for Drug Evaluation and Research. "Compliance with these standards prevents harm to the public."

This action follows Caraco's continued failure to meet the FDA's current Good Manufacturing Practice (cGMP) requirements, which assure the quality of manufactured drugs. Through this seizure, the FDA seeks to immediately stop the firm from further distributing drugs until there is assurance that the firm complies with good manufacturing requirements.

Since January 2009, Caraco has initiated voluntary recalls of drug products to protect the public from potentially defective medications. The recalls involved manufacturing defects, including oversized tablets and possible formulation error.

For more information, please visit www.fda.gov.



Joseph Pickett is Owner and President of Expertbriefings.com, a leading provider of regulatory teleconferences in clinical trials, pharmaceuticals, medical devices and biological products. For more information, please visit <http://www.expertbriefings.com>, or Email: communications@expertbriefings.com.



medidata

Medidata Solutions Worldwide

Technology for a healthy world.™

www.mdsol.com

1.212.918.1847

Are your clinical data systems playing together nicely?

Medidata Rave® leads the industry in EDC, providing effortless interoperability with all your clinical data systems.

But don't take our word for it, CDISC has certified us* on all eight ODM use cases.

Standards make data easy to get in and easy to get out. They take the struggle out of integrations.

Medidata Rave
Sharing doesn't have to be so hard after all...



*Medidata Rave V4.4.2 CDISC V1.1

Current Good Manufacturing Practice for Phase I Clinical Trial Products

The US Food and Drug Administration (FDA) announced a final rule last July regarding the current good manufacturing practice (CGMP) regulations for human drugs, including biological products, to exempt most Phase I investigational drugs from complying with the CGMP requirements. This amendment took effect on September 15, 2008.¹

Via the final rule, the 21 Code of Federal Regulations (CFR) Part 210.2 now includes a paragraph stating that production of investigational drugs for use in Phase I clinical trials conducted under an investigational new drug application (IND) are exempt from compliance with 21 CFR Part 211. This exemption is not applicable to an investigational drug that has been made available for use by or for the sponsor in a Phase II or Phase III study, or if the drug has been lawfully marketed.

According to the FDA, the CGMP update is appropriate because many of the issues presented by the production of investigational drugs intended for use in the relatively small Phase I clinical trials are different from those resulting from production of drug products to be used in the larger Phase II and Phase III clinical trials or for commercial marketing. Moreover, many of the specifications in 21 CFR Part 211 were directed at the conditions of manufacture for drug products beyond the Phase I stage; for example, requirements pertaining to repackaging, relabelling, and stock rotation.

Exemption from the CGMP stipulations does not mean that investigational drugs are excused from any regulatory scrutiny. Even if these products receive the exemption, they remain subject to the statutory requirement in section 501 (a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) that deems a drug adulterated.² This section requires that CGMP terms be met by the methods used in, or the facilities

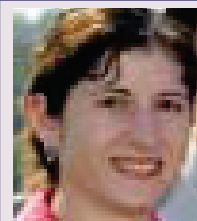
or controls used for, the manufacture, processing, packing, or holding of the drug.

Investigational drugs also remain contingent on the FDA's IND authority. As per 21 CFR Part 312.23(a)(7), among the inclusions required in every IND is a section that describes the composition, manufacture, and control of the drug substance and the drug product.³ Should the FDA determine that a study would expose its subjects to unreasonable and significant risks or that the IND lacks sufficient information to assess these risks, the agency may place the proposed or ongoing Phase I trial on clinical hold (21 CFR Part 312.42(b)(1)).⁴ Termination of the IND is also possible if the FDA finds deficiencies in the methods, facilities, and controls used for the manufacturing, processing, and packing of the drug (21 CFR 312.44(b)(1)).⁵

In parallel with its final rule notification last July, the FDA also issued the Guidance for Industry: CGMP for Phase I Investigational Drugs (Final).⁶ This document is intended to assist manufacturers in implementing manufacturing controls that are appropriate for the Phase I clinical trial stage of development. The following are among the Phase I investigational products to which the final rule applies: investigational recombinant and non-recombinant therapeutic products; vaccine products; in vivo diagnostics; plasma derivative products; gene therapy products; and somatic cellular therapy products. ■

References

1. *Federal Register*: July 15, 2008. Volume 73, Number 136, 40453-40463.
2. Federal Food, Drug, and Cosmetic Act, Section 501(a)(2)(B). Available at: <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAAct/FDCAActChapterVDrugsandDevices/ucm108055.htm>
3. Code of Federal Regulations, Title 21, Part 312.23(a)(7). Available at: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.23>
4. Code of Federal Regulations, Title 21, Part 312.42(b)(1). Available at: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.42>
5. Code of Federal Regulations, Title 21, Part 312.44(b)(1). Available at: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.44>
6. US Food and Drug Administration. "Guidance for Industry: CGMP for Phase 1 Investigational Drugs (Final)," July 2008. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070273.pdf>



Deborah A. Komlos, MS, is the Senior Medical & Regulatory Writer for the IDrac United States (US) Module at Thomson Reuters. Her previous roles have included writing and editing for magazines, newspapers, online venues, and scientific journals, as well as publication layout and graphic design work. Email: deborah.komlos@thomsonreuters.com





Passion & Data 

Biometrics

Insight to innovate clinical trial design. Expertise to deliver high-quality data.
And the dedication to accelerate clinical development.
That's the difference real people bring.

www.kendle.com

Kendle
Real people. Real results.®

Australasia watch

This month in Australasia watch we move our thoughts from Australia to New Zealand, which together with Australia forms “Australasia”. New Zealand, with a population of around 4 million people, largely living in the three major cities of Auckland, Wellington & Christchurch, is a short three hour flight over the Tasman Sea from Australia.

Like Australia, New Zealand offers healthcare companies a pragmatic regulatory/ethics process and a rapid start for clinical trials. All trials need to go through an ethics committee (IRB), but only one ethics committee is needed to cover all sites. If a study is run across multiple regions, it is submitted to the multi-regional ethics committee (MREC), and if sites are all within one region (the country is divided into four regions), the trial is submitted to the local regional committee. There is no fee for ethics committee submissions in New Zealand, with a submission to the New Zealand regulator, Medsafe, costing around US\$4,000 for drug studies. Notably, medical device studies do not need to be submitted to Medsafe, though an ethics committee submission would still apply.

Drug and biotech studies are submitted to Medsafe in parallel with the ethics application and take two to four weeks to approve, and can start subject to ethics approval. Ethics approval can take four weeks at a minimum. Whilst some studies have been approved within 30 days of submission in New Zealand, typically, we advise applicants to allow 6-8 weeks for the submission process. Similar to

Australia, a protocol, investigator brochure, case report form, informed consent form & patient information sheet are required for submission, along with the completed submission forms.

New Zealand offers the following advantages for clinical trials:

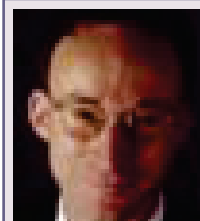
- Low bureaucracy and a practical regulatory environment
- Responsive to changes in requirements as projects develop
- English language environment
- Reverse seasonality and no holiday season in July/August
- Good infrastructure for clinical trial processes & technology
- Standard of medical practice similar to Western Europe/North America
- Lower costs and lower overheads than many northern hemisphere countries
- Quality data to ICH-GCP and FDA standards

Given New Zealand's population, we are often asked what areas of clinical research gravitate our way. Medical devices studies are popular given the lack of regulatory review for such product. Studies can be up and running quickly, often require small cohorts, standards and technology uptake are high, and the work is well received locally and internationally. The same applies for many diagnostics.

Other key areas are indications prevalent in Western populations such as oncology, particularly treatment-naïve studies (versus adjuvant), cardiovascular (both drug and

device) and respiratory studies. New Zealand also has a strong research following in immunology, endocrinology (e.g. diabetes) and in neurology.

Frequently New Zealand and Australia are seen by sponsors as one region (Australasia), as both countries share similar cultures in terms of approachability and clinical trial conventions and standards. Indeed there is often a friendly rivalry in competing with each other to be the first to recruit, with one often being first in the world to recruit due to the regulatory speed described here and in earlier articles. Coupled with a track record of delivering on promised patient numbers, Australia and New Zealand continue to be attractive centres of research excellence in early phase product development and beyond. ■

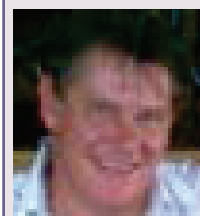


Gerard Dunne

Gerard has worked in Project Management for 20 years in both Information Technology and Clinical Research. He has lived and worked in New Zealand, UK and

Germany. He is currently Managing Director of BELTAS Clinical research, based in Auckland, New Zealand, managing and monitoring studies to provide the data US and local clients need, in New Zealand, Australia and Europe.

Email: gerard.dunne@beltas.com **Web:** www.beltas.com



Russel Neal

With almost 20 years working in the healthcare industry, for the last 16 years Russel has been advising clients in clinical trial management in a career

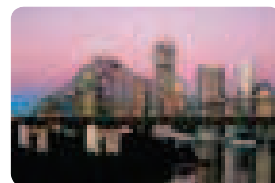
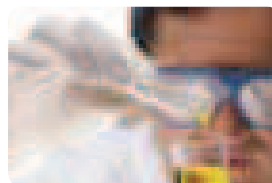
spanning Europe Asia and Australasia. He moved with Quintiles UK to Sydney in 1994 before moving to Singapore in 1999. In 2003, Russel returned to Australia following three years as Regional Training Manager Asia Pacific and is currently Chief Operating Officer at Clinical Network Services (CNS) Pty Ltd, a privately owned, Brisbane based, full service contract research organisation (CRO) providing clinical management support and services to the healthcare community particularly during the early phase clinical development of their products.





Translational
Research Excellence

23 October 2009 | Brisbane, Australia



Join us at the TRX09 in Brisbane, Australia

Early-bird registrations close 31 August 2009.

Stimulating trans-disciplinary interaction and collaborations across all areas of human disease research, drug and diagnostic discovery and development.

Queensland Life Sciences *Globally Engaging Events* include:

Export Awards | Wednesday 21 October

MediQ Breakfast Workshop | Thursday 22 October

Stem Cell Symposium | Thursday 22 October

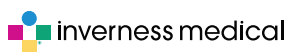
TRX09 | Friday 23 October

Networking Event | Friday 23 October

Investment Forum | Monday 26 October

Please visit www.qctn.com.au and click on the **TRX09** icon for updates and registration to attend the Queensland Life Sciences *Globally Engaging Events*

Thanks to our sponsors as at 11.06.09:



Caribbean watch

The plan to explore the Caribbean as an emerging market to conduct clinical research has included contacting the appropriate country officials including the Ministry of Health and Chief Medical Officer, and discussing the interest in conducting clinical trials in their country. The plan also included obtaining any recommendations, requirements and past and current

experiences, as well as establishing a working knowledge of the process and procedures for obtaining local Ethics Committee approvals. Exploring a relationship with the regional university community was found to be beneficial. The University of the West Indies has three medical university programs in the Caribbean in well populated areas including Jamaica, Trinidad and Barbados. Country officials in Jamaica and Trinidad have expressed general approval to have clinical trials conducted in their locale.

Not to overlook the smaller Leeward island federations: several smaller islands, Grenada, Dominica and St. Kitts and Nevis, have medical universities which are well accredited and recognised. With St. Kitts and Nevis boasting four medical universities, including a nursing school and veterinary universities, exploring the concept of expanding animal studies, first time in human use, pharmacokinetics and pharmacodynamics and other Phase I projects merits further exploration.

Contacts have been made to explore the feasibility of these institutions being involved. It has been found that smaller institutions may exhibit fewer bureaucratic hurdles than the larger university systems. The overall country approval comes from the Ministry of Health from the office of the Chief Medical Officer. Great enthusiasm has been expressed

by St. Kitts and Nevis to explore this further.

There are certain therapeutic areas which could benefit from exploring this region. Clinical trials in the area of cholesterol, endocrinology, diabetes, obesity, tropical related diseases and paediatric trials could be easily completed in a timely manner. Sponsors could have access to data from a population that historically is not well represented in clinical trials. With diseases like dengue fever and accidents and trauma occurring increasingly in the region, clinical trials in these therapeutic areas could prove beneficial.

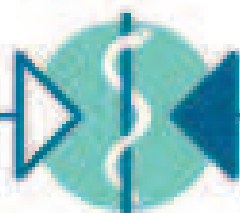
As events impact the economics of the region, establishing a clinical research organisation offers an opportunity on several levels to the local community, an industry to provide human resource training and revenue. With key elements of the recent CSME (Caricom Single Market Economy) travel allowances are intended to benefit the people of the region by providing more and better opportunities to produce and sell goods and services and to attract investment; it enhances the movement of people for medical purposes (including research) which is common to residents of these island nations. Having a medical research tourism hub in the Caribbean is an additional regional asset.

In upcoming editions we will explore additional CRO activities, the cultural response to advertising, ongoing clinical trials and the concept of a Caribbean Phase I unit. ■

Francine Hakim,

BS, CCRA is the president and founder of Caribbean Clinical Research Associates, LLC, a consortium of physicians and health care professionals conducting clinical trials serving the Caribbean.

Ms. Hakim has 15 years experience in the pharmaceutical research industry in business development, project management, full scope of site monitoring, auditing, training and lecturing. If you are interested in learning how your next trial will be conducted in the Caribbean, contact fhakim@caribbeancra.com



MEDILINGUA
TRANSLATIONS

Medilingua BV

Poortgebouw – Rijnburgweg 10

2333 AA Leiden

The Netherlands

Tel: +31 71 5680862

Fax: +31 71 5234660

simon.andersen@medilingua.com

www.medilingua.com

Medical Translators for Clinical Trials

Translation, edit, and review
by experienced, in-country
medical translators

Study Protocols

Informed Consent Forms

Patient Reported Outcomes forms

Summary of Product Characteristics

Patient Information Leaflets

Related services:

Pre-translation source text editing

Translatability assessment

International review management

Harmonization of language versions

User-testing (cognitive debriefing)

Readability testing

Back translation & Reconciliation

Drug Development in China

Relative Regulations on International Multicentre Trails

The last several issues introduced registration of imported drugs, special approval administration and the new-drug monitoring period respectively. With more and more attention being given to performing international multicentre trails in China, SFDA laid down some regulations for international multicentre trails in Provisions for Drug Registration.

Firstly, applications on performing international multicentre trails in China should also follow the drug classification. The applications should be presented according to the requirements of the registration application of imported drugs; the time needed from application to approval is about 6-8 months. Other regulations include the following:

1. Drugs for clinical trials should have been registered in foreign nations, or these drugs should be in Phase I or I clinical trials. SFDA will not accept the applications of international multicentre trials involving internationally-unregistered preventive vaccines presented by foreign applicants.

2. While approving the implementation of international multicentre trails, SFDA can require the applicant to perform a Phase I clinical trial in China first.

3. During the implementation of the international multicentre trails in China, if serious and unexpected adverse events occur in any nation, the applicant should report to SFDA within the time detailed in the relevant regulations.

4. After the completion of the clinical trail, the applicant should submit the complete clinical trail report to SFDA.

5. If the data obtained from the international multicentre trails are used for the drug registration application in China, the prescriptions on clinical trials in this Regulation should be observed, and the complete research data of the

international multicentre trails should be submitted.

The advantages of performing international multicentre trails in China are as follows:

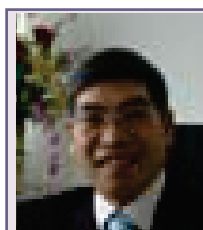
1. China has abundant patients; all kinds of required data can be obtained according to sponsors' demands, and subjects can be rapidly enrolled.

2. In China, sponsors can obtain drug data on Asian people; moreover, the data can also be used for import registration as long as the case amount meets the requirements in the Provisions for Drug Registration.

3. The costs of clinical trial in China are relatively low; therefore, more clinical trial data can be obtained at a lower cost.

Of course, performing international multicentre trails in China has a disadvantage, i.e. the application time is longer than that of other nations. Therefore, sponsors should

communicate with SFDA as early as possible and present applications in advance to ensure the simultaneous implementation of trials in all nations as much as possible. Meanwhile, SFDA is making efforts to reduce the approval time; it is predicted that the approval time can be reduced to 3-6 months in the future. ■



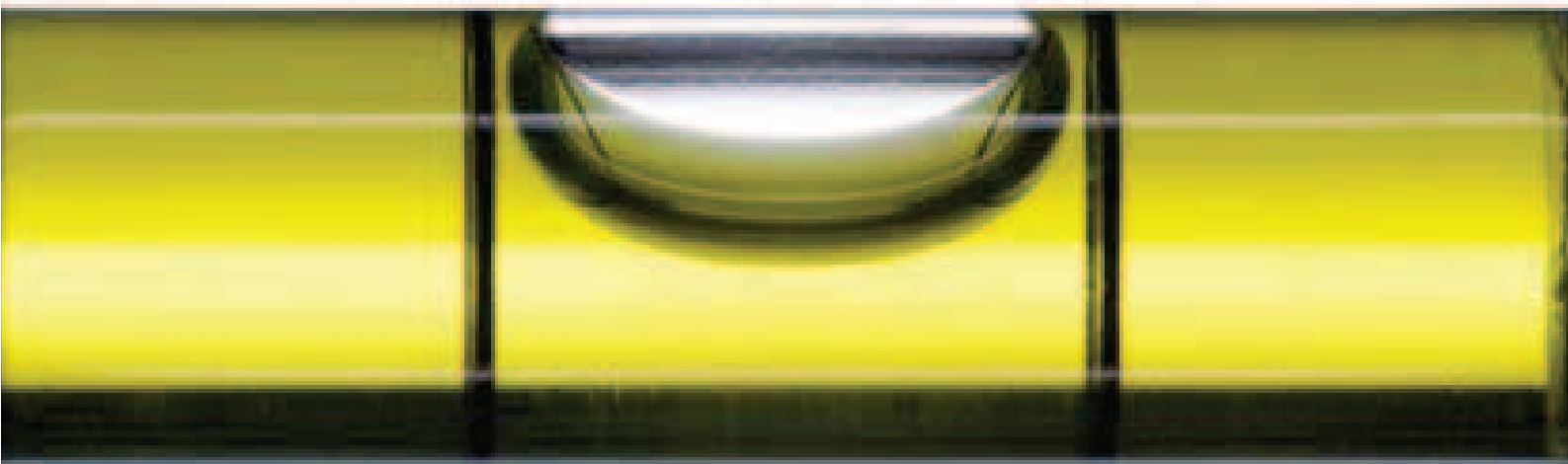
Dr. Xunting Zeng
has decades of
experience in the field
of Clinical Trials. Dr.
Zeng received his PhD at
Kansai Medical
University, Osaka, Japan,
since then he worked as

Special Investigator at International Medical
Centre of Japan. Later he joined InCROM Group,
a Japan based leading international Contract
Research Organization firm. Dr. Zeng is currently
General Manager of InCROM China and head-
ing up to elevate China clinical trial with global
standard.

Email: zeng@incrom.com.cn



more stability



In today's shaky economy, you need a steady partner who will firmly focus on your needs and provide you with the quality, expertise, and responsiveness you require for both your short-term and long-term studies. Throughout our extensive history, our stable business approach has enabled us to maintain an unwavering commitment to our clients by offering a strong portfolio of preclinical products and services, an established global network of resources, and broad industry experience to help accelerate your research and drug development programs both today and tomorrow.

Learn how Charles River can provide the perfect level of support you need at www.criver.com

 **charles river** | preclinical
services

1.877.CRIVER.1
www.criver.com

Clinical Trials Regulatory Process in India

CDSCO (Central Drug Standard Control Organization) is the central authority headed by DCGI (Drug Controller General of India) responsible for the clinical research regulation in India. Following are the key regulations and guidelines which govern the clinical trial regulation in India.

Drugs & Cosmetics Act (1940) and Rules (1945)

Schedule Y: Regulates registration of new drugs and clinical trials (2005 version)

Schedule Y was originally enacted in 1988. However, with the changing global scenario there was need for clinical trial to be linked to status of drug regulations in other countries. In 2005 Schedule Y was amended and following critical changes took place:

- Removal of Phase lag requirements
- Responsibilities of Ethics committees, Investigator and sponsor
- Formats of critical documents

Significant amendments are expected in the next few months in the current Schedule Y.

ICMR Guidelines for Ethical Conduct of Clinical Trials (2006 version)

Indian GCP (2001 version)

CTRI (ICMR Clinical Trial Registry)

Regulatory Approvals for Clinical Trials

Clinical Trial Application (CTA)

T-License (Import License) for study drug

Export License NOC for biological

samples

Clinical Trial Application (CTA) Process

Following Data to be submitted along with the CTA:

- Phase of the study
- Chemical and Pharmaceutical Data
- Animal Pharmacology data
- Animal Toxicology Data
- Data from previous trials
- Regulatory status of drug in other countries
- Regulatory status of trial in other countries
- Number of patients to be enrolled globally
- Number of patients to be enrolled from India
- Number of investigational sites in India
- Affidavits from the sponsor

Documents to be submitted:

- Form 44 and Treasury Challan (CTA Fees: Rs 25000)
- Form 12 and Treasury Challan (Import license fees: 100+50+50....)
- Proposed protocol
- Study subject's Informed Consent
- Document(s)
- Case Record Form

Investigator's brochure
Investigator's Undertaking and
Ethics Committee Clearance, if
available

Supplementary submissions to DCGI e.g.:

i. Approval for the amendments to the protocol e.g. change in inclusion / exclusion criteria or change in sample size, major changes in protocol with respect to study design, dose and treatment options

ii. Notifications for change in no. of sites (Addition/deletion or replacement of sites), amended investigator's brochure, amended informed consent

Streamlining of Clinical Trial Process – December 2006

Global clinical trials classified under two categories:

- Category A: Review within 4-6 weeks
- Category B: Review within 8-12 weeks

Released 'Requirement for filling applications for Global Clinical

Protocol amendment classified into 3 categories

- Category a
- Category b
- Category c

Category a. Those amendments which do not require notification to or permission of the Licensing Authority

- i) Administrative and Logistic changes
- ii) Minor protocol amendments and additional safety assessments in case the institutional ethics committee has already approved these changes

Category b. Those amendments which require notification to the Licensing Authority but need not wait for permission

- i) Additional Investigator sites
- ii) Change in investigator with the consent to withdraw from the earlier investigator
- iii) Amended Investigators Brochure, amended informed consent

Category c. Those amendments which require prior permission of the Licensing Authority

- i) Additional Patients to be recruited
- ii) Major changes in protocol with respect to study design, dose and treatment options
- iii) Any change in inclusion or exclusion criteria

T-License from DCGI for Importing the Drug for Clinical Trial Purpose

- Application to DCGI
- License to import testing quantities of drugs
- Drugs for clinical trial
- Form 12
- Challan

Drug quantity import calculations and justifications

Import License Fees: Rs 100 + 50 + 50.....

NEW PROCESS FOR THE EXPORT OF BIOLOGICAL SAMPLES FOR CLINICAL TRIALS

- Process of Export of Biological samples for clinical trials have been simplified. Since April 2009, there is no need for separate application to the Director General for Foreign Trade (DGFT) for the export of biological samples for clinical trials. Approval / No Objection Certificate now would be granted by the Drug Controller General of India for the export of biological samples.

ICMR CLINICAL TRIAL REGISTRY - Clinical Trial registry was started as optional mode and became advisory from January 2009. However, from 15 June 2009, it is mandatory to register all clinical trials on the ICMR clinical trial registry. Details to include:

- Trial title Inclusion / exclusion
- DCGI approval
- EC approval
- Sponsor details
- Site details

ETHICS COMMITTEE STRUCTURE IN INDIA – AS PER SCHEDULE Y

At least 7 members

Chairman outside institute / One

member outside / one member independent of institute

Appropriate gender

Quorum to decide should have at

least 5 members

- Medical Scientist
- Social scientist
- Clinician
- Legal expert
- Lay person
- Only those Ethics Committee members who are independent of the clinical trial and the Sponsor of the trial should vote / provide opinion in matters related to the study. ■



Kamal Shahani received his Masters in Business Administration from FORE School of Management in New Delhi and also holds Degree in Commerce and Post Graduation in International Business. He has over 20 years experience

in the Indian healthcare and clinical research industry on the senior management positions and has set up and managed large healthcare and clinical research projects. Kamal at present provides specialised market research, business & consulting services and India entry strategy services, including regulatory support services to the clinical research companies from North America. He is also an Honorary Advisor to the leading clinical research education and training companies in India.
Email: info@cliniminds.com

Life Science Logistics – India

At PDP we understand the time critical and temperature sensitive requirements unique to the life science industry. We understand the time pressures and financial constraints of delivering new therapeutics to quality patient groups. PDP has invested its expertise in emerging markets such as Russia and Eastern Europe to provide unrivalled specialist logistic services. We are now pleased to offer the same level of expertise within India.

For further information please contact
the Business Development Team
india@pdpcouriers.com
www.pdpcouriers.com

PDP Courier Services Ltd
Apollo House
Plane Tree Crescent,
Feltham Middlesex
TW13 7HF

T +44 (0)1784 420466
F +44 (0)1784 424300
www.pdpcouriers.com

Key services in India:

- Domestic & International Services
- Next day delivery to US and European markets from all metro and sub-metro areas in India
- Temperature critical shipments monitored with replenishment of dry ice/cool packs en route
- Selection, validation and provision of approved packaging options and temperature controlled solutions
- Services that operate 24/7
- Assistance with correct import and export documentation
- Investigator meeting attendance
- ISO 9001 Quality Assurance

We use our experience to ensure trouble free delivery of your clinical trial materials anywhere in the world, leaving you time to concentrate on the outcome of the trial.

pdpINDIA
SPECIALIST LIFESCIENCE LOGISTICS

Checklist for GMP issues at CROs

CROs, while being well familiar with GCPs, sometimes lack in GMPs as regards standardised procedures for receipt, storage, handling, dispensing and return of study medication as well as qualification of storage units, deviation procedures and documentation. The checklist below may support CROs covering GMP-related issues:

1. Receipt of study medication

Is it defined who at the CRO is authorised to receive study medication, and are these persons properly trained?

There should be procedures in place describing:

- check of delivered study medication for
 - compliance of delivery note with order
 - intact shipment packaging (especially in the case of tamper-proof packaging)
 - instructions accompanying the shipper for storage at CRO
- responsibility for read-out of data loggers
- in which cases study medication should be rejected and the sponsor be informed accordingly.

2. Storage at the CRO

It should be described who is responsible for storing the study medication under the required storage conditions.

There should be procedures in place describing:

- the (immediate) transfer of the study medication to the appropriate storage area
- access control to storage areas
- hygiene and cleaning procedures relevant for the storage area (logbook)
- types of products which may be stored in a storage unit (e.g. not to be used for food)
- documentation of the storage (when, by whom, amount, condition)
- whether unpacking of the study medication from the secondary packaging is allowed
- regular inventory of study medication
- qualification, calibration and monitoring of storage units (including temperature mapping)
- upper and lower temperature limits causing alarm if exceeded
- how to deal with deviations occurring during storage and whom to inform.

3. Shelf-life control and extension at the CRO

It may happen that the use-by date of study medication has to be extended based on stability data available to the sponsor. Although the process of labelling is a manufacturing process basically requiring a manufacturing licence, Annex 13 of the EU GMP guide allows the clinical trial site pharmacist, other healthcare professional, or the clinical trial monitor(s) to superimpose an additional label showing the new use-by date complete with the batch number on the old use-by date, but not on the original batch number.

There should be procedures in place describing:

- how and by whom the study medication stored at the CRO is checked for a valid use-by date, and how the sponsor is informed of expiring study medication

• training of CRO personnel intended for applying a new use-by date label on the study medication

- the procedure, documentation (trial documentation and batch records) and double check of applying a new use-by date label.

4. Dispensing, return and destruction of study medication

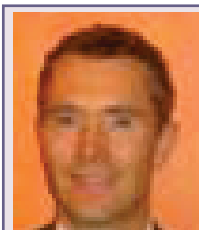
Although the study medication must have been manufactured, controlled and packaged under GMP conditions by the authorised manufacturer, the dispensing CRO is well advised to perform a visual check when dispensing the medication to the patient.

There should be procedures in place describing:

- the visual check for integrity of study medication before handing out to the patient
- how and where to document the dispense
- how to update the inventory after dispensing
- how to handle and store returned medication (used and unused), to reconcile and destroy (if applicable)
- re-distribution of returned unused medication. ■

References

1. *Manufacture of Investigational Medicinal Products, Draft Annex 13, April 11th 2008, EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4.*



Dr. Claudio Alexander Lorck

has over 19 years experience in the field of Clinical Trials Materials Management. Having started his pharmaceutical career

at Fujisawa Deutschland GmbH, Dr Claudio now heads the business unit of "Clinical Trials Materials" of Temmler Werke GmbH.

Email: lorck.c@temmler.eu

Clinical Trial Materials in caring hands



20 years expert knowledge in

Clinical Trial Materials...

... covering the entire supply chain
from Manufacturing to Distribution

- Packaging Design
- Bulk Manufacture
- Sourcing (incl. Import)
- Packaging/Blinding
- Labelling
- Quality Control
- QP Release
- Storage
- Distribution
- Return and Destruction



TEMMLER

Temmler Werke GmbH
Clinical Trial Materials
Phone: +49-89-437299-01
Email: ctm@temmler.eu
www.temmler.eu

What is the line between CRO and sponsor responsibilities?

And the difference between the delegation of tasks and responsibilities?

There is a great need for more professional information on medical, laboratory and technological systems for the development of a new medicament. Medicine development can take approximately 10 to 12 years from discovery to market release. With complicated systems and involved procedures the costs of development of new medicines, have risen dramatically to 900 million dollars. In 2008, 50 billion dollars were spent for clinical research. This expenditure and the associated workload increases every year. The allotted budgets and duties for R&D by the pharmaceutical and biotechnology companies get transferred to outsourced clinical research organisations.

The costs and savings associated with pharmaceutical companies are dictated by,

- the requirement for medicine to reach rapidly to market;
- the increase of sophisticated diagnostic and treatment methods being applied;
- the necessity of working with experts and experienced teams in almost all fields.

Independent organisations that support sponsors during drug research and development are called CRO's - Clinical Research Organizations. CRO legally may represent sponsors.

Clinical research study may include a team of other organisations. The difference between organisations such as Site Management Organisations (SMO), Clinical Trial Management Organisations (CTMO) from the CRO is that here instead of the sponsor, the researcher may transfer some tasks to organisations, but these organisations legally do not represent the researcher.

Today, pharmaceutical companies can transfer any operation relating to drug development from pre-clinical laboratory tests through to phase 3 studies to outsourced organisations.

Outsourcing provides great advantages to the pharmaceutical manufacturer, it allows for better control costs which are especially critical when deciding whether to continue on a project when initial results were negative, or not conclusive.

The growth of the CRO has its origins in the increase in number of trials in different cultural centres. The requirements for greater diversity of data means greater need for more volunteers, in turn means more specific regulations.

The numbers of CRO's started to increase in the early 80's fuelled

by the increasing demands offered by pharmaceutical companies. Continued increase in numbers of CRO's has resulted in extended services.

CRO services:

Product development

- Formulation, production
- Clinical Research Management (Pre-clinical-phase IV)
- Clinical, medical, security monitoring
- Toxicology
- Bio-analysis
- Laboratory Services
- Data management
- Bio-statistics
- Consulting services associated with Government agencies
- Licensing procedures
- Medical text writing, translation services
- Medicine management (production, packaging, labelling, storage, distribution, collection, disposal)
- Randomization services
- Researchers and central services choice

CRO's have a diversity of structure ranging from full service organisations to organisations specialised only in one field.

CRO choice:

The fact that these services are offered and the sponsors do acquire these services does not necessarily mean that research and development becomes faster or achieved at lower cost, since standards must be maintained.

Clinical Research must be done based on the written rules of:

- ICH-GCP, Declaration of Helsinki, GMP, GDP, Local Regulations and guidelines

According to ICH-GCP related to the CRO;

• **5.2.1 The sponsor may transfer all or a portion of duties and functions associated with its own to the Contract Research Organizations. However, the ultimate responsibility of the quality and accuracy of research data always belongs to the sponsor. Contract Research Organization has to apply quality control and quality assurance systems**

- **5.2.2 Any task or function transferred or taken over from the**



Clinical Research Organization

Analytical Biochemical Laboratory BV (ABL BV) is an independent contract laboratory and a central laboratory serving (multicenter) clinical trials for pharmaceutical and biotechnological companies. ABL is a laboratory that operates world-wide, supporting clinical trials and pre-clinical drug development studies (PK/PD and safety samples).

ABL is subdivided into two departments

Bio Analytical Services

Focuses on the analysis of samples derived from pre-clinical and clinical studies. Available techniques include:

- LC-MS/MS
- GC-MS
- GC-FID, NPD and ECD
- HPLC with UV, fluorescence and electrochemical detection
- Immunochemistry (RIA, EIA, FIA)
- Clinical chemistry
- Hematology

Contact: Mr. E. Oosting MSc, technical director

E-mail: eoosting@abl.nl

Clinical Trial Services

Offers support services for the conduct of multi-site clinical trials ranging from sample logistics and source verification to data and project management.

Contact: Mr. H.J. Trip, manager CTS

E-mail: htrip@abl.nl

By combining these two activities, ABL is able to optimize the overall efficiency, quality and data integrity while saving costs and time. We operate under a set of strict protocols and procedures to ensure transparency whilst not affecting the capability to adapt to the requirements and needs of the individual client.

Analytical Biochemical Laboratory BV

W.A. Scholtenstraat 7

P.O. Box 232, 9400 AB Assen

The Netherlands

Telephone: +31 (0) 592 34 42 11

Fax: +31 (0) 592 34 44 25

www.abl.nl



Contract Research Organizations has to be specified in writing.

• 5.2.3 The responsibility of any task or function specially not transferred or taken over from the Contract Research Organizations belongs to the sponsor

• 5.2.4 Refers made to the sponsor in the user guide, to the extent of task or function transferred or taken over from the Contract Research Organizations also does include the Contract Research.

According to the perspective of authority, no matter from where the sponsors have received service, what kind of agreements were made, all final responsibility regarding the reliability of the quality of work and of data belongs to the sponsor.

As a result, the sponsor has to be sure of the quality of service received and having required experience and knowledge of the duties, that are transferred from SAK. For this reason, many sponsors have created criteria to work with CRO who have these competencies.

Some of these criteria are;

- Experience from similar projects of the CRO
- experience with similar sponsors of the CRO
- for how much years the CRO is working in this area
- organization structure of CRO
- training and experience of staff with clinical research
- Experience and infrastructure of High level managers
- Are Quality systems applied (customer, employee satisfaction, etc.)
- Basic training programs
- Are Emergency action plans made?
- Supervision and hiding conditions of Working documents
- Compliance and information with local regulations
- Audit and accreditation
- Software used

Research has shown that after the implementation of the above-

mentioned selection criteria, the sponsors make their decisions according to priorities given below.

- Having the capability to apply Problem detection and analysis process (problem-solving processes to be defined, recovery plans, etc...)
- Compliance with Project-specific practices
- Team chemistry integration (work ethics, a general approach, etc...)
- Experience of CRO (relevant experience with projects, contribution of the leading team to the project etc...)
- Capacity of CRO (geographic coverage, etc. ...)

Making a contract with the CRO:

The sponsor after primarily determining needs of its own research has to make a contract with the CRO for the transfer of tasks related to these services.

This contract has also to contain;

- Legal issues such as contract work directive, the service time, time of payment, amount, etc (obligations, insurance, termination, choice of law, privacy, bad management etc.).

Working directive (services to be taken from outside must be explained with all details.)

For example;

- the scope of work
- responsible personnel
- timing
- payment schedule, phases, cost / budget
- the desired formats for reports
- list of CRO that will be used
- data base, etc...
- risk sharing
- protocols
- special requirements for work etc.

CRO Responsibilities:

- CRO training programs should be created for new joining Organisations
- If services should be taken from outside, assessment process should be available.
- CRO training programs should be created for service taken from People/ organizations from outside.
- It should have appropriate personnel, infrastructure and facilities to meet the requirements of the project.
- It should have the necessary software to monitors and measure Project management and performance.
- It should be made sure that the insurance made by the sponsor is appropriate.
- The application file provided by the sponsor should be careful reviewed and compliance must be ensured.
- It should be made sure that Medicines process is managed well (place and conditions of the place where drugs are being manufactured, in which conditions they are stored, how the distribution is made, shelf life, tags, etc.).
- For Protocol or research brochure revision, process must be defined.
- If there is transfer of the task, it must be well documented.
- Routine quality control of the system must be created.
- It must be made sure that the SOP which the sponsor wants to be applied are the recent revisions.
- Tel/ fax numbers given by the sponsor necessary for the security alert, fax numbers should be tested.

WHICH CAME AS THE BIGGER SHOCK? THE SCALE OF THE DISASTER OR THE FACT IT WASN'T COVERED?



At Chubb, we understand the importance of the small print. Our specialist life science underwriters and loss control engineers are all industry experts. They know the international regulatory environments and can offer business-specific loss prevention and risk management advice. Backed by Chubb's experience and global reach, our flexible new life science policy provides tailored cover that evolves with your business. And if the unthinkable does happen, specialists within our award-winning claims team respond within 24 hours of your call and pay within 48 hours of a settlement. With so much at stake, what price peace of mind?

We are designed to be different. We are Chubb Insurance.



Argentina Australia Belgium Bermuda Brazil Canada Chile China Colombia
Denmark England France Germany Hong Kong India Ireland Italy Japan Korea
Mexico The Netherlands Puerto Rico Scotland Singapore Spain Sweden
Switzerland Taiwan Thailand United States Venezuela

Telephone: +44 (0)20 7990 5000 www.chubb.com/uk

- CRO by third parties (e.g. specialist Biostatistics, medical monitors, etc...) should have data management system to make active data transfer / review easier.
- CRO must continuously develop their technological capabilities.
- CRO are required to issue and follow-up compulsory working documentation. For this process they should have a system for archiving

Cro- Sponsor Relation:

There is no doubt that the key factor to the success of the project is to work with a correctly selected CRO. However, even if the choice is correct, for the results of this cooperation to be positive it is necessary that the parties manage to work together in harmony.

Looking on the difficulties experienced between the sponsors and the CRO, it can be seen that the majority reasons for problems are based on facts such as being from different company cultures, not working in the same physical location, not fully understanding expectations and services to be given and differences in experience and competence.

To conduct a successful collaboration;

- It has to be defined and understood how and how often, from whom, and in which conditions communication and reporting related to CRO- Sponsor- Research Center- 3rd Servicing institution at the head of the project will be made.
- Duties of Sponsor and CRO should be listed at the beginning of work, parties must act within the framework of these duties, and they should not interfere in each other's tasks.
- It is accepted that the Accepted SIY (SOP)s have been understood by the working team and that the parties do act according to agreed SIY's. As communication is inevitable during the project, it is important that the project team leaders at determined times make status assessment, and do sincerely share information and if necessary establish an emergency action.
- The sponsor and the CRO have to be aware that the

successful resultant project is the common goal. All parties should mutually, with empathy listen to each other and assess advice and recommendations

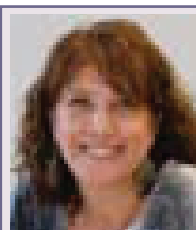
The rapid growth in generic drug area that is envisaged in the next 5 years, even today makes pharmaceutical companies feel the pressure, the original drug patent expiry time being expired, with time portfolios in medication will decrease. All this increases the importance of drug research and development efforts. If we compare the pharmaceutical companies with CRO research and development experience, they will start to take an increasing role in research and development, with their cost-effective and standardized services.

In summary, the increase in the required expertise and experience of research and development work and therefore increase of cost will further increase the tasks and duties of the CRO's.

Ethical standards in clinical research are applied with precision. It will not be difficult for researchers, sponsors and CRO's -who are professional practitioners, to act with honesty, fairness and follow basic ethical standards. These basics being pre-condition of clinical research together with patient's security will also bring further quality assurance. ■

References:

1. *Applied Clinical Trials*, 2. *Visiongain Ltd. Global Clinical Trials Business*, 3. *Report & Analysis*, 4. *Unithink Easy Solutions*, 5. *Reilly Center, University of Notre Dame*, 6. *Promedica evaluation*, 7. *Premier Research*



Sule Mene, MD CEO, MENE RESEARCH

Sule Mene graduated from Medicine Faculty in 1992 and practiced medicine in Turkey. She held several core positions in different pharmaceutical companies and international CROs respectively CRM in MSD, both Medical Manager and CRM in Abbott Laboratories, Ingenix, i3 Research, Head of Clinical Management in Lundbeck,

Sule Mene is founding partner of MENE RESEARCH which was set-up in 2003. She is the Board Member of the Association of Clinical Research in Turkey since 2006.





Medinet

*Eurofins Medinet
Shanghai.*

Now CAP Accredited!



safety biomarkers bioanalysis microbiology genomics safety biomarkers bioanalysis microbiology genomics safety biomarkers bioanalysis microbiology genomics safety biomarkers bioanalysis microbiology genomics safety biomarkers bioanalysis microbiology genomics safety biomarkers bioanalysis microbiology genomics safety biomarkers bioanalysis microbiology genomics

Global Laboratory Services. **Discover. Experience.**

Offering the synergy of integrating
a broad range of global central laboratory services

Very strong focus on Asia with owned facilities
in China and Singapore

www.eurofinsmedinet.com

info@eurofinsmedinet.com

Breda - Paris - Washington DC - Denver - Singapore - Shanghai

East and West - Clinical Trials in CEE

Introduction

With 15 % annual growth predicted in the CRO industry in Eastern Europe (CEE) between 2008 and 2012, the region has positioned itself as an attractive region for performing clinical research, and has become a high-quality and cost-effective option for companies with drugs in development.

Of course, with more than 20 countries, it is unrealistic to describe the CEE in general terms, but there are common elements that make these countries attractive, including: ready access to patients, good cost benefits, and high quality of data. An established network of qualified and experienced investigators and clinical staff is always key, and this applies especially in non-traditional regions, where quality and ethical standards must be cultivated to ensure compliance with accepted global standards

Quintiles has been a pioneering clinical research organisation (CRO) in CEE (and parts of the Middle East), having been the first global CRO to conduct trials there, and having played a significant role in establishing ethical and scientific standards for clinical investigators in the region.

Since 1996, when Quintiles first began operations in Vienna, Austria with six people, CEE has grown its talented and engaged workforce to more than 1500 people in 21 countries.

Between 2002 and 2007, the number of Form FDA 1572s filed in CEE countries increased from 3.8 % to 7.9 % . Central and Eastern Europe now represents the largest number of global clinical trial initiations outside of North America and Western Europe.

Now with 1500, Quintiles remains the leading CRO across Central and Eastern Europe.

Still growing, but not emerging any more; the regional environment CEE has a population of more than 400 million people in 21 countries, 13 of which are EU members. All of the countries work to ICH-GCP guidelines and several have implemented the EU Clinical Trials Directive. But countries that have implemented the EU directive still carry local regulations requirements, which can prolong and complicate the regulatory process. In addition some countries have various other local bureaucratic barriers which may interfere with the regulatory process and startup activities, so there is still scope for improvement in streamlining the process

CROs working internationally must fully understand variations in geography, culture and population size across the region: for example, that large countries such as Russia Ukraine and Poland cover about 70 % of the regional population. In addition, they must understand the major differences which exist in terms of maturity of the economy, healthcare market, and clinical research industry between these countries.

The EU countries all have at least ten years of clinical research experience. These countries have established economies and cannot be considered emerging countries anymore, although they still maintain the CEE advantages for clinical trials, having enthusiastic, experienced investigators, good access to patients and good quality of data. Timelines of the regulatory authorities are usually clear, and logistical processes are predictable and streamlined.

Some countries, mainly the more eastern countries, are still in the growth phase but are expected to grow fast.

Non-EU countries such as Russia and Ukraine have the greatest growth potential. With a population of 141m in Russia and 46m in Ukraine, both countries have the potential to keep on growing beyond their existing regional market share. Most of the clinical activity here is performed in the main cities, but the Russian authorities have approved sites outside the main cities, which will lead to additional growth and expansion of clinical research activity.

The Baltic countries are relatively newer to the clinical research arena, but have succeeded in establishing a professional environment for clinical development. Finally, Belarus, Georgia, Kazakhstan Uzbekistan and other more eastern previous Soviet countries are at the emerging stages of entering the market.

As countries and regions become involved in the clinical trial process there is inevitably a startup phase, and this is often driven by CROs. During this period it is important that regulators, investigators and patients are fully informed about the clinical research process and the role clinical trials play in developing new and better medicines. This creates a positive environment for conducting studies and ensures early adoption of international standards.

With its large population and patients' pool, CEE still has good potential for growth. Along with responding to significant variations in economic status, market maturity language and culture across countries, there are other challenges that must be addressed, including:

- Logistics and drug storage and delivery, requirements for custom or samples shipment
- Problematic electronic infrastructure that may restrict use of communication tools such as the internet, phone lines and computer-related systems. This may expand the work needed or result in more site-specific expenses
- The large and growing population has led to demand for sites out of the main cities. Although there are obvious benefits associated with these opportunities, access to these sites may be a challenge if monitors are based in the cities
- The growing market results in growing competition. In such an environment, a CRO may have trouble maintaining appropriate levels of trained staff to ensure quality remains high. CROs need to maintain vigorous training programmes, implement QA procedures and manage staff attrition.

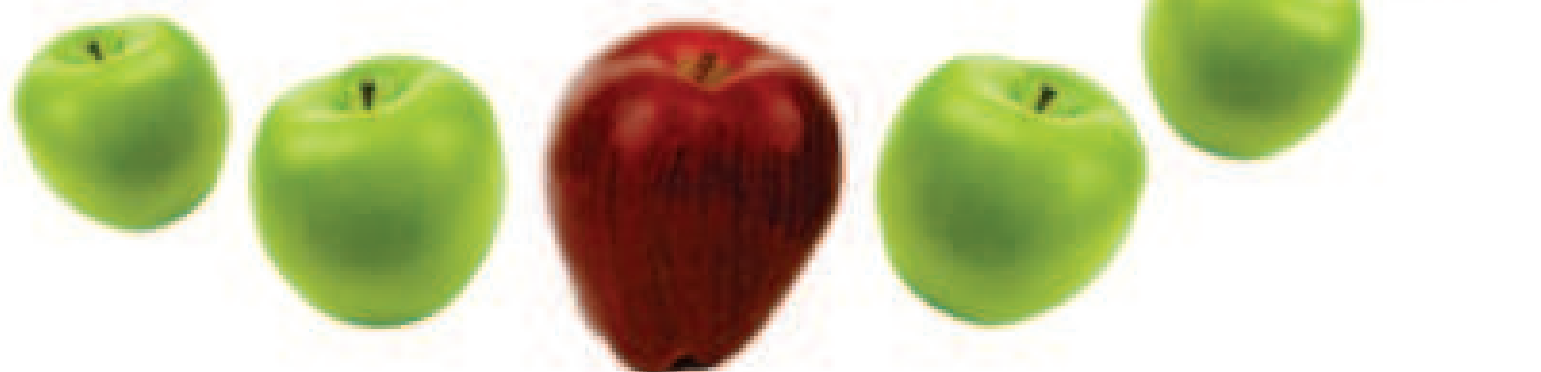
Organisations conducting clinical trials in Central and Eastern Europe need deep understanding of these issues and adequate infrastructure to be successful. Then they must effectively apply their knowledge and experience to ensure unity of work across countries in order to make the most of the region's access to patients, cost benefits and quality data standards.

Access to patients

Recruitment rate per site is much higher in CEE than in any other region - sometimes up to ten times higher than in western sites. Hundreds of thousands of patients have been recruited into global studies in the CEE region in the last decade.

CONGENIX

COMPLIANCE RELIABILITY OPPORTUNITIES



Congenix is an expert Contract Research Organization represented in the US and EU, operating within the Commonwealth of Independent States (CIS) including Russia, Ukraine, Byelorussia, as well as the CEE.

Congenix offers its clients an integrated package of customized services in Phase I-IV clinical trials:

- Protocol and subject recruitment feasibility assessment
- Investigator selection and investigational sites' qualification
- Regulatory affairs (regarding the countries in the CIS and CEE)
- Study supplies custom clearance, warehousing and distribution
- Project management and clinical monitoring
- Data management based on using the SmartPen™ technology surpassing both paper and web-based EDC systems approaches
- Biostatistics
- Site management and contract administration
- Quality assurance and quality control
- Investigator training

Congenix's advantage consists of a beneficial combination of experience, a deep knowledge of local issues within our geographic area and an unique approach based on adaptive processes and technology developed by Health Decisions™ (www.healthdec.com)



Congenix, LLP
361 Falcon Way
Menlo Park, CA 94027 USA
Phone: 810-799-8764
Fax: 810-799-8924
e-mail: stephen.solomon@congenix.com

Our data shows that more than 42 % of our sites enrolled more than ten patients in a shorter time period than in other regions (compared to 17 %, 19 % and 12 % in North America, Western Europe and Asia Pacific respectively) in a lower enrolment period. Moreover, CEE has fewer sites that recruit zero patients than other regions.

Table 1: Average patient enrolment duration, Phase II-III

The largely centralised structure of healthcare provision and the highly specialised centres of excellence in healthcare have been factors in creating an environment so conducive to clinical trials, and differentiates CEE from other emerging regions such as Asia and Latin America.

Centralised healthcare systems, with large hospitals and specialist outpatient clinics covering either large populations or specific diseases or both, mean that there is greater patient volume in one place. It is also easier to identify these patients, due to comprehensive databases kept by these specialist centres.

Hospitalisation is more frequent for procedures that would usually be performed in outpatient clinics in western countries. As a result, accessibility of patients is high, while some administrative and financial obstacles are taken out. This leads to faster recruitment because there is a higher chance of finding the right patients for each specific study.

The region proposes a large pool of treatment-naïve patients which can assist customers where there is a need to research a new medicine in previously untreated patients. Patients themselves benefit from participating in clinical trials as they get access to expert investigators and specialised clinics and are treated by respected physicians. As a result, they are paid close attention by healthcare professionals involved in their care, therefore compliance with medication regimes is high.

Enthusiastic investigators are still ready to learn and adapt to international regulatory requirements, and are also motivated to have access to potential new treatments to improve their patients' care.

In summary, both patients and investigators benefit from participating in clinical trials, and at the same time there is the potential to develop medicines more effectively given a faster enrolment period compared to other regions.

Quintiles differentiates itself in the region by having a strong regional presence, working successfully with local competent authorities and providing tailored logistical solutions in each country. Internally, there are groups of local experts who have in-depth knowledge of each country's regulatory requirements and specific trial logistics issues.

Since Quintiles started its activity in the region, it has enrolled 145,000 patients in 13,500 sites (1996-Q108), gaining expertise in all therapeutic fields and creating a pool of over 14,000 experienced and motivated investigators. This database helps to track sites and ensure that they are

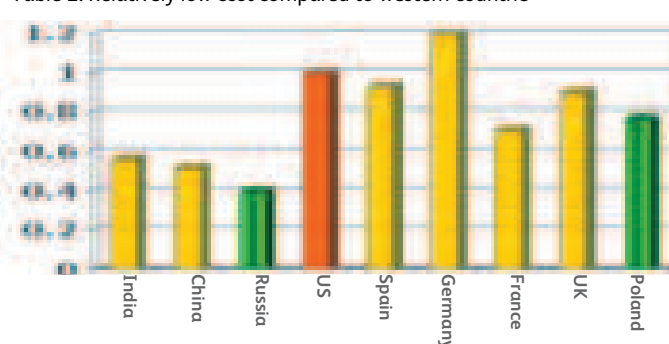
Table 1: Average patient enrolment duration, Phase II-III

	Treatment duration (months)	Number of patients	Number of patients/month	n
CEE	22	728	33	11
Western Europe	27	1,4	1	1
Asia Pacific	27	1,4	1	1
North America	27	1,4	1	1
Total	27	2,8	1	1

Sample: Phase II and III CNS, diabetes and cardiovascular multi-centre clinical studies, in one region only, comparably sized.

Source: Tufts CSDD analysis of FDA's Bioresearch Monitoring System (BMIS)

Table 2: Relatively low cost compared to western countries



Clinical Study Cost Comparison by Country (indexed to US cost) – Source: Fast Track Systems

Table 3, Number of US FDA Data Audit inspections by year and by the geographic regions, For Cause inspections are not included here since they are predominantly made on US sites: n=923 or 98.5 %

Data Audit	North America	Latin America	Europe	East Europe	Middle East	Africa	Asia	Oceania	Total
Year	n	n	n	n	n	n	n	n	n
Unknown	1	0	0	0	0	0	0	0	1
1977	30	0	0	0	0	0	0	0	30
1978	69	0	0	0	0	0	0	0	69
1979	143	0	0	0	0	0	0	0	143
1980	190	5	0	0	0	0	0	1	196
1981	205	0	1	0	0	0	0	0	206
1982	161	0	0	0	0	0	0	0	161
1983	174	0	0	0	0	0	0	0	174
1984	224	0	1	0	0	0	1	0	226
1985	208	0	4	0	0	0	0	0	212
1986	178	1	0	0	0	0	0	0	179
1987	218	0	2	0	0	0	0	0	220
1988	238	0	1	0	0	0	1	0	240
1989	184	0	11	0	0	0	0	2	197
1990	220	0	5	0	0	0	1	0	226
1991	208	0	7	0	0	0	0	0	215
1992	253	0	11	0	1	0	0	0	264
1993	181	0	15	0	0	0	0	1	197
1994	171	0	17	2	0	2	0	0	192
1995	301	1	22	2	0	0	0	0	326
1996	372	4	18	1	1	0	0	3	398
1997	288	2	34	1	0	2	1	0	328
1998	255	1	32	8	0	3	2	0	301
1999	285	2	37	4	0	3	1	4	336
2000	250	1	30	5	1	6	0	0	293
2001	206	5	18	3	0	3	1	0	236
2002	200	7	8	2	0	2	3	0	231
2003	204	7	15	15	0	2	0	0	243
2004	179	13	30	18	0	2	3	1	246
2005	252	15	26	8	0	2	4	0	307
2006	242	9	22	28	0	2	11	2	336
2007	174	14	24	35	0	2	10	0	259
2008	167	5	11	23	0	2	0	0	208
Total	6,640	92	402	155	5	33	39	14	7,375
1997-2008, n	2,777	87	287	150	7	31	36	7	3,364
%	82.1	2.5	8.7	4.5	0.0	0.9	1.1	0.2	100.0

Source: US FDA Site Inspection Findings, 1997-2008, Fail to Justify Globalization Concerns, Clinical Trial Magnifier, April 2009.

well equipped and the medical facilities are at the highest level, that communication tools are available and that high treatment standards are maintained.

Quintiles' growth is a consequence of organic growth and not a result of merging or acquisitions, which results in our ability to apply the same management cultures and standards in all countries – both the matured and the newly emerging. With more than 447 studies delivered in the last five years, the company makes a significant contribution to the growth of the region.

Cost benefits

This high patient recruitment and accelerated enrolment rate leads to greater efficiencies in the development process, reducing time and cost. This benefit combines with lower fees for ethics committee authorities, investigators and hospital, lower costs for specific procedures such as CT and MRI fees, and lower patient reimbursements, and results in significant cost savings for international studies. Table 2 compares the clinical cost by country:

Table 2: Relatively low cost compared to western countries

Keeping high quality data

Alongside fast growth, accelerated enrolment and relatively low cost, the Central and Eastern Europe region has a proven history of keeping high quality data. CEE investigators are well-trained, familiar with ICH-GCP and the EU Clinical Trials Directive, fluent in English, and comfortable working to international standards.

A report by Johan PE Karlberg, MD, PhD, BSc, published in Clinical Trial Magnifier in April 2009 evaluated US FDA site inspection findings from 1997 to 2008. It identified common deficiencies and compared inspection findings across the globe.

Karlberg found that Eastern Europe has the best overall results, with "only 3.3 % of Eastern Europe site inspections reporting three or more deficiencies." This compares with an average of 20.2 % for Europe, 13.1 % for North America and 6.5 % in the rest of the world.

Europe averaged 1.30 deficiencies per site inspection, compared with 1.02 for North America and 0.71 for East Europe.

Table 3, Number of US FDA Data Audit inspections by year and by the geographic regions, For Cause inspections are not included here since they are predominantly made on US sites: n=923 or 98.5 %

These figures are reassuring to Quintiles' customers, who can confidently undertake a clinical trial there, while benefiting from working with the only fully-integrated service provider in the industry combining clinical, commercial, consulting and capital. This means consistency in data management and reporting, project management and laboratory testing, as well as experience and a demonstrated track record of excellence in safety and ethics and an unwavering commitment to patients.

The current economic situation has affected growth in the region, however according to The Economist, Business Outlook CEE, paper 93 April 2009, the health and pharma sector retains positive growth potential for 2009 and 2010. ■



Janos Filakovszky, MD, PhD, is Managing Director, Vice President Eastern Europe & Middle East. The majority of his clinical trial experience has been in large-scale, multi-site Phase II and Phase III studies researching treatments for such maladies as depression, stroke, neuropathic pain, Parkinson's disease, epilepsy, diabetes, breast cancer, and cerebrovascular and cardiovascular disorders.

EXAM[®] Packaging

Our Solutions

Polyurethane Boxes

- Polyurethane foam injected in coated, water-resistant cardboard
- Different wall thicknesses to meet various insulating requirements (24 hours and more)
- All boxes can be used with dry packs or dry ice

Isolainers

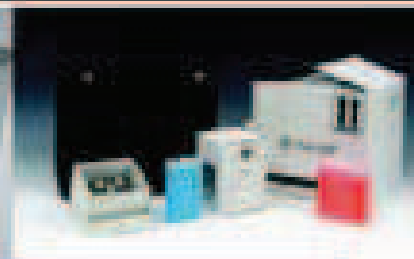
- Insulated boxes in polypropylene
- Interchangeable insulating walls in polyurethane foam

Dangerous Goods Packaging

- In accordance with IATA, IMDG and ADR/RD regulations and specifications
- Various officially validated solutions available for toxic or infectious products and Biological substance samples

Cooling Agents

- Non-toxic
- High performance



Testing Centre

Our testing facilities meet the highest norms in cold chain management equipment:

- Norm 21 CFR Part 11 compliant
- AQB certified
- Temperature range between -40 and +60°C
- Testing according to existing standards (such as ISIRI, WHO, ...) or specific temperature profiles

tel: +32 (0)24 607 155 - www.exampackaging.com

EXAM[®]
PACKAGING

Challenges & Options in the Conduct of Clinical Trials in Emerging Countries in Africa and the Caribbean

Abstract

Clinical trials are studies performed with human subjects to test new drugs or combinations of drugs, new medical devices, new approaches to surgery or radiotherapy or procedures to improve the diagnosis of disease and treatment, thereby increasing the quality of life of the patient. Maintenance of data integrity in clinical trials involves special challenges and requirements. Therefore, the experience of the sponsor/CRO, abilities/experience of the chosen investigators, adequate equipment and the past experience of the clinical trials site personnel are some of the very important criteria that will determine the success of the clinical trial. In this article, we will initially describe some of the challenges that can be encountered in the conduct of clinical trials in emerging markets in Africa and the Caribbean. Afterwards, we will propose some options to address some of these challenges including, but not limited to, examining the different technological options that can be put in place to facilitate the increase in clinical trials activities in these marginalised areas of the world.

Introduction

Many African and Caribbean countries fall into the category of developing nations which are defined by the Wikipedia Dictionary as “countries with low standards of democratic government, civil sciences, industrialization, social programs and/or human right guarantees.” Most of these countries have poor quality healthcare and few, if any, health education services. Additionally, there is an increase in migration as a consequence of the many challenges the world is facing today. This places an additional strain on an already over-burdened healthcare system and makes it difficult to follow subjects who may wish to participate in clinical trials.

New drug development requires multiple resources which are often lacking in developing nations. These are in the form of human, financial and material resources. Due to these difficulties, most African and Caribbean countries rely on drugs that are being tested in developed countries to be imported into their countries with minimal

or no testing among the developing countries’ own populations.

However, there have been recent efforts to conduct clinical trials and training in several countries in Africa and the Caribbean. In the last 10-20 years, many of these countries have made the transition from the category of “developing” nations to “emerging” nations. In comparison to developing nations, the term emerging nations, per Wikipedia Dictionary, is used to describe “a nation’s social or business activity in the process of rapid growth and industrialization. Such countries are considered to be in a transitional phase between developing and developed status.”

The required standards for conducting research on new drugs are not always able to be met in both developing and emerging nations. Additional factors that must be taken into consideration when implementing clinical trials and training in these countries are: lack of facilities, government policy interference, non-indigenisation policy, poverty, ignorance, diseases, corruption, communication problems, and insufficient and inexperienced personnel, to name a few. We will go on to examine each of these and their effect(s) on the conduct of a clinical trial.

Challenges in conducting clinical trials in developing countries

Developing countries in Africa and the Caribbean often do not provide an environment that accommodates the conduct of clinical trials. However, with adequate commitment from a sponsor/CRO, NGOs and other governmental agencies, it is possible to conduct clinical trials and training in emerging countries.

The ability to have effective communication is paramount to the success of clinical trials. Internet access is an important tool along with the use of mobile phones, personal digital assistants (PDAs), e-mail and the use of communication software such as Skype, Google Talk and NetMeeting. These are all excellent tools with which to facilitate effective communication. The internet can be used in various phases of a clinical trial. This can include: recruitment and screening of

“A general lack of strong government policies for the protection of human subjects creates problems with the protection of the rights, safety and wellbeing of potential clinical trial participants.”

potential participants, follow-up with a participant at a remote site, completion and transmission of the evaluation forms (case report forms) to follow the participants' course and any possible treatment side-effects and so forth. Unfortunately, many parts of Africa and the Caribbean still lack the reliability of these resources, which poses a significant problem for the conduct of clinical trials and training.

Non-supportive government policies and non-indigenisation policies can also have an effect on the conduct of clinical trials. A general lack of strong government policies for the protection of human subjects creates problems with the protection of the rights, safety and wellbeing of potential clinical trial participants. The more recent debates on the ethics of doing research in developing countries have centred on three main issues. Firstly, how to define the standard of care to be used in research in developing countries. Secondly, the availability of successful trial interventions after the study ends. Lastly, the development of an informed consent that meets international standards for this "at risk" population. The persistence of the controversies on these issues reflects, in part, conflicts in the interpretation of existing ethical guidelines which are sometimes contradictory or rely on questionable ethical standards. Some examples of these are the various non-indigenisation policies that currently exist.

Other factors that have direct and indirect effects on the conduct

of clinical trials in Africa and the Caribbean are: lack of training, inexperience, insufficient personnel, poverty, ignorance, corruption and language barriers. The vast majority of the clinical trials in developing countries today are run by trained and experienced personnel from the developed world because there are not enough local people with the training and experience to do so. The

majority of the population in Africa and the Caribbean lives in rural areas. Add to that poorly maintained roads, inadequate facilities, unreliable or non-existent water and power supplies, various diseases, lack of education and financial resources with no phone or internet capabilities. These factors combined create a situation ripe for the introduction of investigator bias, misconduct and fraud. This further demonstrates the need for effective collaboration between private (e.g., entrepreneurs, NGOs and corporations) and public sectors (e.g., government) as a necessity to effectively conduct clinical trials in these countries.

Addressing some of these challenges

Most of the African and Caribbean countries have very modest financial resources to support funding for biomedical research and clinical trials at the present time. The establishment of a networking system among the developing, emerging, and developed countries is a way to get the dialogue started and provide opportunities to share experiences. Further, the implementation of

“Non-supportive government policies and non-indigenisation policies can also have an effect on the conduct of clinical trials.”

an improved biomedical sciences educational system would provide opportunities for the indigenous peoples to help in the medical modernisation of their respective countries. The developing countries need also to establish acceptable data collection methods that meet the international standards, but that are sensitive to local cultural issues. This will help assure acceptability of the data collected if it is used as part of a submission in an EU country or the United States.

The governments of these developing countries have their own role to play in the protection of indigenous peoples. Governments can assist by helping to eradicate poverty, improving general education and health education status, as well as bringing about improvements in the government's infrastructure and the implementation of policies that are in the best interest of their citizens.

Development of a Consortium between African and Caribbean Countries

Biomedical research requires access to a great many resources that would not normally be within the modest financial means of many African and Caribbean countries. However, if they were to pool their resources as a consortium, they would be able to conduct clinical trials that would meet international standards. The funds could be used to provide the financial resources to develop personnel, build world class hospitals and research facilities, provide clinical trial training and purchase equipment. Caligeo Clinical Trials Initiatives (CCTI) is an example of a non-profit organisation that has taken the initiative in providing this type of service to local populations in countries in African and the Caribbean at subsidised rates in recognition of some of the financial constraints among these countries.

Creation of a Network between African and Caribbean Countries

The consortium mentioned above should establish a network with developed countries in order to facilitate their ability to conduct internationally acceptable clinical trials. The consortium members can benefit from the knowledge gained from these associations by increasing their knowledge of the clinical trial process. An example in which an indigenous NGO effectively collaborated with a consortium of developed countries and expertise to promote clinical trials is noted in the article "The New Wave of Development Infusion in the Clinical Trials Industry in Nigeria" (Journal for Clinical Studies, January 2009, pp. 32-33). Developed countries may also assist by providing financial support for clinical trials in these developing countries as well as additional training for local personnel and contributions to the improvement of the local medical facilities. This assistance can improve the quality of the data retrieved and help provide for the protection of human subjects, while increasing the globalisation factor of the clinical trial. Once again, government involvement is an important factor in determining whether or not developed nations will be willing to provide their support for these types of projects.

Biomedical Sciences Education System and Clinical Trial Training

Education is one of the best ways to improve the healthcare system in any country. Although it would be ideal to have multiple

biomedical research institutes throughout Africa and the Caribbean, it may not be practical or realistic in some countries. A significantly less expensive and feasible alternative is the implementation and expansion of clinical trials education at both the secondary and university educational levels. Educating the younger generations in the clinical trials process will instil confidence among Big Pharma in the likelihood and sustainability of conducting clinical trials in these

regions. Since clinical trials involve human risk, educational training should never be compromised. A comprehensive, sustainable, and repeatable means of training should always be explored when conducting any type of clinical trial education.

While some of the emerging nations in Africa and the Caribbean have already taken steps in building biomedical research institutes, it is important that such development be constructed very deliberately. Buildings without proper infrastructures will crumble easily. The most important infrastructure that is needed for a biomedical research institute to sustain itself is education. As emerging countries in Africa and the Caribbean instil confidence among Big Pharma in their respective regions, it is also important that local governments play an active role in ensuring that treatment

IND, Phase III and Phase IV trials are actively conducted among these countries before embarking on Phase I and II trials which are typically more inherently risky than their counterparts.

Conclusion

There have been growing efforts to conduct clinical trials and training in some countries in Africa and the Caribbean. In part, this is due to the realisation of some "developing countries" transitioning to the category of "emerging nations". While some advancements have been made, especially among these emerging nations, there is still a lot more to do to ensure sustainability of these efforts and, more importantly, safety of the people in these countries regardless of whether or not they are involved in clinical trials.

In this article, we described some of the special challenges and offered some suggestions to effectively conduct clinical trials in emerging nations in Africa and the Caribbean. In summary, the continuing establishment of national and international consortiums and networks will help developing and emerging countries provide clinical trial data that meets international standards as well as bringing increased opportunities for these countries to participate in global new drug and device development. ■

"Biomedical research requires access to a great many resources that would not normally be within the modest financial means of many African and Caribbean countries."



Gbolahan Fatuga

is the founder of Caligeo Clinical One Vision, an international non-profit Clinical Research Organisation (CRO) with the primary objective of promoting clinical trials throughout Africa and the Caribbean. Fatuga received his M.Sc. in Drug Regulatory Affairs and Health Policies from Massachusetts College of Pharmacy and Health Sciences, and a B.Sc. degree in Neuroscience from Brown University. He is an active member of the International Faculty Advisory Board for the Association of Good Clinical Practices in Nigeria (AGCPN) and a member of the Nigerian Association of Pharmacists and Pharmaceutical Scientists in the Americas (NAPPSA). Email: gfatuga@gmail.com.

The China Clinical Trials Outsourcing Congress

28-29th September 2009, Midland Hotel, Manchester, UK

China is at the forefront of the increasing trend to use so-called emerging markets where clinical trials can cost substantially less than those in Western countries.

However, the decision to outsource clinical trials to China requires an understanding of the scientific and regulatory procedures in China and a thorough knowledge of the implications involved.

KEY TOPICS TO BE ADDRESSED:

- Assessing the real value of incorporating China into a multinational clinical trials strategy
- Strategic and regulatory considerations before conducting clinical trials in China
- Considerations involved in designing the China component of the trial to position the drug for eventual China market approval
- The China SFDA has been working more closely with regulatory bodies and industry leaders to improve processes and approval times. Is this still an obstacle and what changes have been made?
- What are the concerns for small and medium pharma and biotech companies conducting clinical trials in China without operations in the country?

OUR EXPERT PANEL OF SPEAKERS INCLUDES:

- **Dr. Xunting Zeng Ph.D** – General Manager, InCROM China
- **Ying Luo, Ph.D** - Chairman and CEO, Shanghai Genomics, Inc, Chairman and CEO, GNI Ltd
- **Prof. Leung Ping** – Cheng, Director of the Institute of Chinese Medicine, Chinese University of Hong Kong
- **Zheng Qin Yin MD& PhD** - Professor and Director of Southwest Eye Hospital
- **Senior representative from SFDA**
- **Dr. Yiding Xing** – Director of Pharmacovigilance, Excel PharmaStudies Inc
- **Dr. Frank Lu** – Director of Bioinformatics, Excel PharmaStudies Inc

The congress provides an opportunity to learn first-hand how to outsource preclinical and clinical trials to China and to meet and network with over 20 Chinese CROs and Hospitals actively involved in conducting preclinical and clinical trials.

REGISTER BEFORE 14TH AUGUST AND SAVE £305 PER DELEGATE

For more information about registration or to enquire about sponsorship and speaking opportunities please go to www.globalengage.co.uk or phone +44 (0)1865 479232

Alternatively, please contact Steve Hambrook, Conference Director, at steve@globalengage.co.uk





Therapeutic Cancer Vaccines and the Need for Innovative Approaches

A serious need exists to define medical paradigms characterised by innovative approaches and “modernisation” of tools to advance the development of promising medical products. Particularly in the development of products for serious and life-threatening diseases (e.g. cancer), researchers often find that while clinical data suggests only marginal benefit in the intention to-treat (ITT) analysis, there exists a smaller, select subset of patients who appear to show significant clinical benefit. For example, for effective therapeutic cancer vaccines, a clear benefit has been demonstrated for patients who can successfully mount an immune response to the vaccine as measured by a significant antibody response after dosing. At the same time, the safety risk of administration of such therapeutics is generally low. Unfortunately, prospective determination of patients who will mount the immune reaction required is impossible because specific immunogenicity cannot be measured until after administration of the drug. Identification of the covariant factors that determine the host’s ability to produce an immune reaction and the extent of that immune reaction have not been identified for most therapeutic cancer vaccines. Strategies that address the challenges faced in the development of therapeutic cancer vaccines include the following:

- Additional consideration of positive risk-benefit ratio
- Consideration of appropriate clinical trial design
- Development of alternative methods for evaluating treatment comparisons

A new generation of targeted therapeutics for the treatment of cancer is emerging from the growing knowledge base of biomedical drug discovery. Based on a biological approach, novel cancer therapeutics currently under development include agents in the areas of vascular targeting, antisense, gene transfer, immunotherapies, and apoptotic induction. These innovative treatments hold the promise of improved therapeutic choices for selected cancer patient populations and have the benefit of diminished side effects compared with traditional cytotoxic therapies. A review of these programmes indicates there is no optimal solution for determining clinical benefit for therapeutic cancer vaccines by targeting therapies to approach patient subpopulations under current drug development paradigms. Greater consideration and appreciation of the positive risk-benefit ratio, consideration of alternative and more appropriate clinical trial designs, and expansion of prospective definitions of subpopulations would clearly facilitate further development of these promising therapies.

Brief Overview of Cancer Vaccines in Development

Therapeutic cancer vaccines specifically targeted to epitopes on tumours are relatively new tools in the fight against cancer. Cancer vaccines are generally composed of tumour cell epitopes, known tumour growth factors, or tumour cell DNA, and are designed to stimulate the patient’s immune system to produce antibodies against the desired molecule. In effect, the vaccines are designed to use the host’s own defenses to attack or starve the tumour, resulting in an anticipated

outcome of inhibition of disease progression and increased survival. Several types of therapeutic cancer vaccines[1, 2] are currently under development, including the following:

- Whole tumour cell
- Gene-modified tumour cells
- Plasmid (naked) DNA
- Peptides (including antibodies or antibody stimulators)
- Viral gene transfer vectors
- Antigen-modified dendritic cells

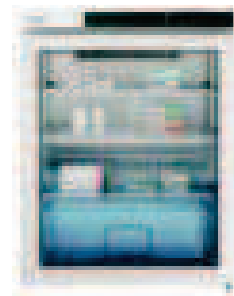
Although cancer vaccines represent a very active area of development worldwide (as of 6 July 2004, www.cancer.gov listed 13 cancer vaccines in clinical development – by 4 June 2009 the number of trials focused on cancer vaccines for treatment had risen to 290 in the United States [US] alone), few cancer vaccines have been approved globally.

Cancer Vaccine Development Consideration #1: Risk-Benefit Ratio

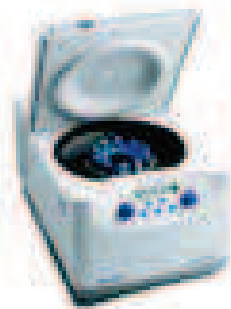
In clinical drug development, the risk-benefit ratio is a measure of the risk of doing harm or injury compared with the potential therapeutic benefits of administration of the drug. The FDA has the stated mission of promoting the protection of the health and safety of the US public through continual review of the safety, efficacy, and quality of data of premarketed and postmarketed products and weighing of the risk-benefit ratio. The risk-benefit ratio varies depending on the condition being treated. For example, in the case of life-threatening illnesses (e.g. cancer), the acceptable risk for a drug may be higher than those for non-life-threatening illnesses (e.g. conjunctivitis).

Cytostatic agents, such as most immunotherapeutics, generally do not show the same efficacy profile as cytotoxic agents. Although cytotoxic agents are designed to eradicate cancerous cells, cytostatic agents are expected to halt further progression of the disease and cause only limited tumour regression. By their mechanism of action, vaccines are intended to act as cytostatic agents and may show an additive or synergistic effect when treated in combination with cytotoxic agents such as standard chemotherapy. Consequently, significant tumour regression may be difficult to achieve with vaccines or other immunotherapeutics or targeted therapies alone. The current approach to define a surrogate endpoint of efficacy related to tumour response (by WHO [World Health Organization] or RECIST [Response Evaluation Criteria In Solid Tumors] guidelines) is tailored to tumour reduction or shrinkage by cytotoxic agents, as measured by the proportion of patients showing a complete or partial response. In light of their expected cytostatic activity, the clinical benefit of therapeutic cancer vaccines should include stabilisation of the disease, as defined by increased time before disease progression.

In contrast to cytotoxic agents that generally show pronounced risks with respect to their safety profile, cytostatic agents offer significant advantages to patients in terms of improved tolerability and can be used as adjunctive or maintenance therapy in biologically relevant patient populations. As cytostatic agents, cancer vaccines generally show relatively benign safety profiles with the most frequently reported adverse experiences typically including flu-like symptoms, generalised



Medical
Refrigeration



Refrigerated
Centrifuges



Patient
Monitoring



ECG
Machines

Providing an Effective Cure For All Your Clinical Trial Equipment

Medical Equipment Supplies offering Purchase and Hire options
Equipment Service, Calibration, Repairs and Recycling
Sourcing Solutions for your Clinical Trial Equipment
Medical Equipment Management Outsource Programme

Offering the Lowest Total Cost Solution

tel. +44 (0) 1257 225469



www.mesm.co.uk • sales@mesm.co.uk

pain, myalgia, fever, and administration site disorders (injection-site pain and granulomas at the injection site).

The risk-benefit ratio of immunotherapeutics and cancer vaccines should be evaluated in a systematic way in the context of the clinical condition that they are designed to treat. For example, in patients who have the appropriate biological marker, the benefits of Melacine® (melanoma vaccine of tumour lysates, approved for use in Canada but not the US) vaccine administration are marked, while the safety risks to patients lacking the marker are minimal. Cancer vaccines that provide meaningful clinical benefits for antibody titer positive patients and offer minimal risks to antibody titer-negative patients should be prioritised for both approval and use.

Cancer Vaccine Development Consideration #2: Clinical Trial Design

The standard ITT analysis requires inclusion of all patients randomised in the study regardless of whether the patient received the study drug. The basis of the ITT analysis is to avoid misrepresentation of the clinical data. Specifically, in the case of noncompliance and dropouts, exclusion of patients could lead to biasing of the study findings if the noncompliance or study withdrawal was because of side effects, failure to improve, or any other factor that is related to outcome. The ITT analysis assumes that an appropriate patient population can be prospectively identified via well-defined inclusion and exclusion criteria. In the case of cancer vaccines, this necessitates inclusion of patients who lack the appropriate biological sensitivity and fail to mount a specific immune reaction, such as a rise in antibody titer. Although ITT analyses are undoubtedly useful in determining efficacy for most investigational products, consideration of other types of analyses is necessary when evaluating the clinical benefit of therapeutics for which the mechanism of action is dependent upon a specific biological response and the risk associated with the administration of such a product is minimal.

Although progress is being made, particularly by applying genomic and proteomic definitions of patient samples, large patient populations are needed to identify those patients that can benefit or who are particularly receptive to an immunotherapeutic compound. In this regard, the approval process for Iressa® (AstraZeneca) is illustrative. Iressa was initially approved based on a marginal clinical benefit in refractory non small-cell lung cancer patients. During and after the approval process, further research in patients who received the drug as part of a large compassionate-use protocol, showed a consistent and marked benefit in a small (10% to 15%) subpopulation of patients who had a single gene mutation. Such identification of an efficacy population is highly beneficial for selective treatment and further understanding of targeted therapy of this product class. However, this approach is impractical in the current development of most targeted therapies because of the inherent limitations of traditional trial designs coupled with a relatively scarce fund of knowledge regarding the widespread potential for the interplay between drug product and (or effects of) biological and physiological factors built during early research and development stages.

The placebo-controlled parallel-group design is one of the most common trial designs employed for the evaluation of a drug's efficacy. Using this traditional design for the evaluation of cancer vaccines has often proven to be a major barrier to the development of these products because clinical benefit is only expected in a select subpopulation of patients (i.e. benefit is expected only in those patients who mount an antibody response [titer-positive] to the vaccine). The overall clinical benefit in patients treated with the therapeutic cancer vaccine compared with those treated with placebo masks a selective efficacy in the immunoreactive subpopulation. The inability to determine prospectively which patients will be titer-positive creates a significant, if not insurmountable, hurdle for the development of some cancer vaccines. Detecting significant overall efficacy, not simply in a subset of patients, necessitates the conduct of large clinical trials that are often infeasible because of the sizeable financial investment,

extended timelines, limited availability of patient population, and high risks of failure to which all drugs are subject (e.g. a new drug entering Phase 1 only has an 8% chance of reaching the market[3]).

Study designs for the development of an immunotherapeutic agent could include initial assessment of the patients' immune function. However, such general immunogenicity tests are not predictive of specific immunoreactions (i.e. rising antibody titers) towards a specific antigen or epitope. Alternatively, all patients entering a trial could initially be treated with the immunotherapy; responders who mount the specific antibody titer would then be randomised for additional treatment (Figure 1). This study design is attractive in that it identifies those patients who produce antibody titers before randomisation, and therefore provides a selective immune reactive subpopulation for evaluation.

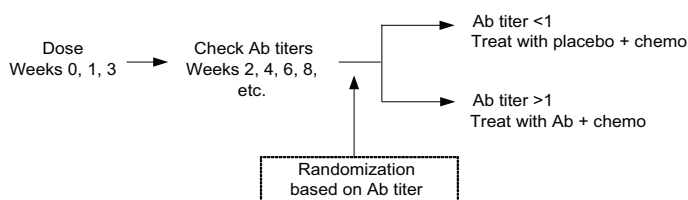


Figure 1. Alternative immunotherapeutic study design.

Variations on this design are possible, such as providing an initial immune challenge with the therapeutic cancer vaccine and then randomising based on the antibody titer only after patients are shown to be refractory to the standard of care chemotherapy. Unfortunately, it is difficult, if not impossible, to demonstrate the clinical benefit of additional dosing in such study designs, because this would require demonstration of the benefit of primary dosing versus multiple follow-on doses of the vaccine. Moreover, in the case of therapeutic vaccines intended to treat cancer patients with a short life expectancy (e.g. as in advanced pancreatic cancer) only a few patients are likely to receive more than three doses of the vaccine.

Because of the limitations noted for potential study designs, the best design appears to be the traditional prospective, parallel-group design. However, in the case of cancer vaccines, in addition to the ITT analysis, other types of analyses should also be considered when evaluating the clinical benefit. Specifically, in addition to the direct comparison of active treatment and placebo or standard therapy, a subset analysis that compares benefits in patients who are antibody titer-positive with those of patients who are antibody titer-negative should be considered. A prospective identification of antibody titer positive patients for a preferred analysis should be valid as a primary efficacy endpoint because patients who do not generate an antibody titer could therefore not be expected to receive clinical benefit from the vaccine. An additional analysis to demonstrate the validity of the selection of the antibody titer-positive population would include comparison of the patients who received placebo with an alternative method of treatment group comparison or imputational analysis (see Cancer Vaccine Development Consideration #3 below).

Cancer Vaccine Development Consideration #3: Alternative Methods for Evaluating Treatment Comparisons

As the previous examples show, it is oftentimes impractical to prospectively identify predictive markers that define immune-reactive patients (i.e. baseline covariates, such as demographics, baseline performance status, laboratory values). An imputational analysis provides an option to define subsets of "would be immune reactive" or "placebo immune reactive" patients, and therefore, is a useful alternative. Future progress on using imputation of data and consideration of genomic and proteomic innovations should also be considered when looking at supporting efficacy findings in studies of cancer immunotherapeutics and vaccines.

Determination of which patients within the placebo arm of the study would have mounted an antibody titer is not possible without

administering the drug to placebo patients (and thereby invalidating the placebo control). To improve the "comparability" of the placebo arm to antibody titer-positive patients, putative antibody titer-positive patients in the placebo arm can be identified by randomly selecting from the placebo population a subgroup of the placebo patients and comparing the survival curves or other efficacy endpoints of these "placebo titer-positive patients" with the known antibody titer-positive patients' log-rank statistics. This process of random selection of subgroups of placebo patients and analysis is repeated many (e.g. 10,000) times to approximate the true distribution of the p-values of the comparison. If statistical evidence of a difference between the two treatment groups is present in a significantly large proportion of these simulated samples, then it is plausible that these differences are due to treatment with the antibody generating compound, even though the true set of "placebo titer-positive patients" in the control arm is unknown. The specific structure and parameters for the imputational analysis may be prospectively defined in the statistical analysis plan and developed in a dialogue with the FDA.

The imputational analysis proposed above provides a framework to identify parameters that may predict the immune responders in controlled studies of immunotherapeutics. In addition to positive-trending ITT and preferred analyses of subpopulations, the imputational analysis should provide sufficient evidence that the drug is efficacious. Accelerated approval of immunotherapeutics and cancer vaccines based on the proven efficacy using predefined imputational analysis together with the low risk of such treatment provides an improved path for clinical development of such compounds. Based on these findings, Phase 4 studies may follow that can verify the efficacy in the selected population.

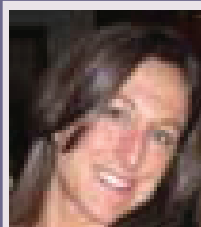
Accelerated approval with Phase 4 commitment is an attractive answer to the development challenges for therapeutic cancer vaccines that show significant benefit in subset populations and have positive risk benefit ratios. Phase 4 protocols would allow the conduct of trials

large enough to see clinical benefit in the ITT population. However, under the current review paradigm, acceptance of subanalyses and demonstration of efficacy in Phase 4 commitment protocols cannot be applied in the cases outlined because currently, Phase 4 studies are only initiated to confirm Phase 3 efficacy of surrogate endpoints.

In the interim, it may be valuable to assemble the FDA and various sponsors of therapeutic cancer vaccines with products in Phase 3 or Phase 4 development to exchange innovative approaches about the unique challenges faced by these products. Specifically, use of the statistical approach outlined above and other possible statistical or experimental design options could be discussed in a cooperative manner to help identify meaningful prospective parameters and possible surrogate endpoints with the aim of accelerating the development of promising therapies for these life threatening diseases. ■

References

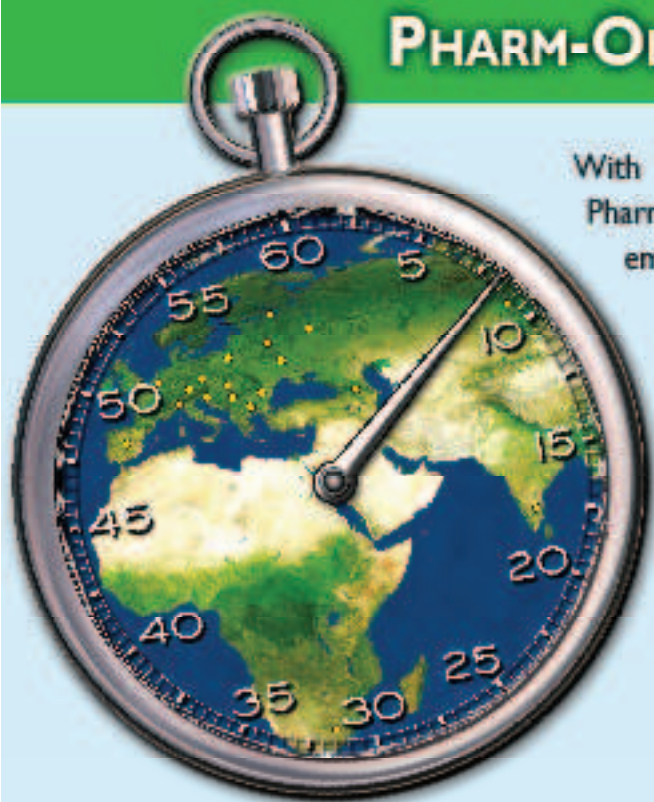
1. Berzofsky JA, Terabe M, Oh S, Belyakov IM, Ahlers JD, Janik JE, et al., *Progress on new vaccine strategies for the immunotherapy and prevention of cancer. J Clin Invest*, 2004. 113(11): 1515-1525.
2. Bitton RJ, *Cancer vaccines: a critical review on clinical impact. Curr Opin Mol Ther*, 2004. 6(1): 17-26.
3. Gilbert J, Henske P, Singh A, *Rebuilding big pharma's business model. The blockbuster business model that underpinned big pharma's success is now irreparably broken. The industry needs a new approach, In Vivo: the Business and Medicine Report*. 2003. 73-80.



Dr. Jennifer R. Weidman, Ph.D., R.A.C. currently serves as Senior Director of Research and Development for Cancer Advances Inc. and Regulatory Scientist for Cato Research Ltd. She received her doctorate in genetics from Duke University in Durham, North Carolina, and has more than 10 years' experience in scientific research.

Email: jweidman@cato.com

PHARM-OLAM REDUCES TIME TO MARKET



With 25 offices among the world's most populated cities, Pharm-Olam International provides cost effective coverage in both emerging and traditional markets for Phase I to IV studies.

Since 1994 we have used our local knowledge of an investigator's past performance, competing studies, and regulatory environment to offer sponsors an accurate and informed plan to complete trials on time.

We provide full service or strategic outsourcing across all therapeutic areas. Contact Pharm-Olam for a complimentary feasibility study for your next clinical trial.

USA: +1 (713) 559-7900

UK: +44 (0) 1344 891121

info@pharm-olam.com

www.pharm-olam.com

POI Pharm-Olam INTERNATIONAL
A Contract Research Organization

MONITORING • REGULATORY • BIOSTATISTICS • DATA MANAGEMENT • PHARMACOVIGILANCE
MEDICAL MONITORING • PATIENT RECRUITMENT • PROJECT MANAGEMENT



Vaccines:

preventive and therapeutic vaccines and adjuvants on the rise.

Background

There remain major areas of unmet medical need which could be addressed by further research and development into preventive and therapeutic vaccines. Additionally, there are seemingly never-ending challenges for vaccine manufacturers to overcome emerging and re-emerging infectious diseases with preventive vaccines. There is also strong demand for the development of therapeutic vaccines in patients with autoimmune- and allergy-based disease, linked to high tumour incidences and growing evidence of resistance to standard chemotherapy regimes.

Reaching these goals may require new and improved adjuvants for the development of more effective and more powerful vaccines, especially in immunocompromised populations.

Preventive vaccines

Within the last 50 years enormous progress has been made in vaccine development. The global mortality due to life-threatening infectious disease is estimated to have been reduced by approximately two million deaths per year through the use of vaccines. In developing countries, where hygiene standards could be improved further, vaccines against rotavirus, pertussis, diphtheria, measles, polio, tetanus and tuberculosis have all contributed to reducing unnecessary deaths (1).

The first worldwide immunisation program began in 1974, when the World Health Organization (WHO) set out to eradicate poxvirus-induced diseases; one of its other aims was to promote the acceptance and increase the usage of additionally available preventive vaccines. The Global Alliance for Vaccines Immunizations (GAVI) founded in 2000, reinforced these messages, resulting in dramatically increased worldwide vaccination rates from 21% in 1980 to 84% in 2006 for tuberculosis, diphtheria-tetanus-pertussis, measles and polio (2). However, despite such overwhelming evidence of the benefits of immunisation, many countries still only recommend their use and challenges remain (3).

Major public health challenges that could be tackled, at least in part, by vaccination include: Human Immuno-deficiency Virus (HIV, an ongoing pandemic since the early 1980s), Severe Acute Respiratory Syndrome (SARS) pandemic in 2003, caused by the SARS-Coronavirus paired with an as yet undefined avian influenza virus; arthropod-borne virus (Arbovirus) epidemics such as the Chikungunya virus and the West Nile Fever Virus (WNV) and malaria.

Virally-induced tumours were originally described in the 1920s when Rous demonstrated virus-associated sarcomas in chickens (4). In 2008, Harald zur Hausen was awarded the Nobel in Medicine Prize for the discovery of the role of Human Papillomaviruses (HPV) in the etiology of both squamous cell carcinoma and adenocarcinoma of the cervix (5). HPV vaccines have been available since 2006 (initially in the US and more recently in Europe), which help contribute to elimination of the contracted viruses and significantly reducing the incidence of subsequent (approximately 10 to 20 years later) cervical carcinoma. Vaccines designed for conventional (intramuscular, intravenous or subcutaneous) application as well as alternative routes of application, e.g. intranasal, when combined with the need to target special populations e.g. pediatric, elderly and the immunocompromised,

may require special development focus on adjuvants to optimise efficacy and safety profiles of the vaccine.

Different types of vaccines

Most vaccines possess little or no inherent immunostimulatory property and require adjuvants to elicit a potent immune response (6). Vaccines can be classified into eight groups, based on their manufacturing process (recombinant versus native purified versus modified/inactivated), the nature of antigen (protein versus synthetic peptides and DNA) and their complexity (inactivated versus live attenuated, and peptide versus protein):

Box 1: Design of preventive vaccines

- Recombinant vaccines (proteins) produced by genetic engineering (e.g. HPV, Hepatitis B)
- Conjugated vaccines (polysaccharides joined to immunostimulating molecules)
- Polysaccharide vaccines (containing bacterial surface sugar moieties e.g. pneumococcal vaccines)
- Subunit vaccines (specific proteins purified from whole proteins, e.g. seasonal influenza vaccines)
- Toxoid vaccines (inactivated toxins, e.g. diphtheria, tetanus)
- Inactivated vaccines (containing whole portions of killed bacteria or viruses, e.g. Salk polio and Hepatitis A vaccines)
- Live, attenuated vaccines (weakened viruses or bacteria, e.g. Sabin polio and Bacillus Calmette Guérin (BCG) vaccines)
- DNA (deoxyribonucleic acid) vaccines (i.e. genes encoding human proteins)

All of these vaccines need to be designed to meet efficacy and safety profiles, while the adjuvant formulation for the vaccine may impact on the pharmacokinetic and pharmacodynamic profiles.

Preventive vaccines should ideally have one or more of the properties as described in box 2.

Box 2: Anticipated prominent effects/mechanism of action of preventive vaccines

- Induction of protective immune response
- Enhancement of humoral immunity / antibody-mediated (Th-2 type)
- Induction of neutralising antibodies
- Enhancement of cellular immunity / T-cell mediated (Th-1 type)
- Induction of cytotoxic T-lymphocytes (CD8+)
- Induction of NK (Natural Killer cells) and LAK (Lymphokine-Activated Cells)

Therapeutic vaccines

Therapeutic vaccines are aimed at individuals already suffering from a specific disease with the intention to cure or alleviate the condition by eliciting a specific, beneficial immune response. The majority of therapeutic vaccines - targeting oncology indications - are based on monoclonal antibodies directed against tumour-associated antigens or against key molecules involved in pathological signal transduction pathways or processes. There is growing evidence that patients with chronic and/or persistent viral diseases may benefit from therapeutic vaccines. Patients with AIDS (Acquired Immuno-Deficiency Syndrome), Hepatitis B or C virus infections, HPV infections or those persistently

infected with herpes viruses could benefit from a reduction in the disease burden or the potentially fatal consequences of chronic viral persistence. In addition, for some viruses there is no efficient chemotherapy available (e.g. for HPV (papilloma virus) or Epstein-Barr Virus (Herpes virus)), or patients may be “non-responders” to standard chemotherapy regimens, and therapeutic vaccines could be beneficial.

According to a report published by the Pharmaceutical Research and Manufacturers of America (PhRMA) in December 2008 (7), more than 633 “cutting edge” medicines are currently in development for more than 100 diseases, with a focus on cancer and related diseases (30 %), infectious diseases (18 %) and autoimmune disorders (10 %). The report lists vaccines (30 %), monoclonal antibodies (mAb, 20 %) and other medicines such as the antisense technology, cell and gene therapies, growth factors and interleukins, recombinant proteins and others (6) as potential therapeutic modalities. In addition to mAb, other new medicines are in development as an alternative to first-line chemotherapy treatment. Most mAbs currently approved by the Food and Drug Administration (FDA) or European Medicines Agency (EMA) are indicated for first and/or second-line therapy and/or in combination with conventional chemotherapeutics (8).

Box 3: Therapeutic areas of interest vaccines are being developed

- Oncology (lymphoid and solid tumours)
- Infectious diseases (e.g. HPV and Hepatitis B)
- Autoimmunity (Rheumatoid Arthritis, Multiple Sclerosis, Systemic Lupus Erythematosus (SLE), others)
- Allergy
- Neurodegenerative disorders (e.g. Amyotrophic Lateral Sclerosis, AML)
- Genetic disorders (Cell and gene therapy, ATMP)

The major target for therapeutic vaccines is TNF-alpha, which has a pivotal role in regulating anti-inflammatory cytokines (including IL-10, sTNFR and IL1Ra) and pro-inflammatory cytokines (e.g. IL-6, IL-8, GM-CSF, 9). There is currently a focus on hemato-oncological cancers by targeting “cluster of designation” or CD-proteins on the surface of immunocompetent cells, e.g. CD20 cells

Table 1 illustrates some commonly used monoclonal antibodies for cancer treatment (American Society for Cancer, 10; additional information from EMA European Public Assessment Report website, 11).

The PhRMA Biotech Report 2008 suggests an increase of new mAbs

approved by FDA/EMA in the near future, if sponsors demonstrate safety and efficacy in clinical trials.

Box 4 highlights some desirable anticipated effects of therapeutic vaccines.

Box 4: Anticipated prominent effects / mechanism of action of therapeutic vaccines

- Enhance / augment immune response
- Induce apoptosis in target tumour cells
- Antibody-dependent cell-mediated cytotoxicity (ADCC)
- Complement cytotoxicity (CT)
- Activate of T helper function at site of tumour
- Modulate of regulatory T-cells
- Break tolerance (shift from Th-2 type to Th-1 type)
- Induce class switch from IgE to IgG4 (allergy)
- Interfere / inhibit specific kinases / kinase-substrates
- Inhibit proliferation
- Block receptor-mediated signalling
- Increase chemosusceptibility
- Induce enhanced cytokine secretion

Adjuvants

Adjuvants have been used for decades and are intended to improve the immune response to immunisation. They enhance, accelerate, or prolong the immune response by triggering key molecules of the innate (rapid onset of effect, non-specific and transient) or the adaptive (slower onset of effect, antigen-specific and anamnestic through memory B- and T-cells) immune response pathways. Adjuvants may also be classified by their primary interaction with key molecules and/or signal transducers of innate immunity e.g. Toll-Like-Receptors (TLR) or cellular elements in the adaptive immune response, e.g. dendritic cells, B- and T-lymphocytes. Thus, adjuvants may trigger the rather selective cytokine production. Cytokines are of major importance, especially considering the basic models of the TH1/Th2-type paradigm, which allows through polarising cytokines and their relative concentration either to induce the Th1-type (T helper 1 cells) immune response (cell-mediated) or the Th2-type (T helper 2 cells) immune response (humoral or antibody-mediated) immunity (12, 13, 14).

On the other hand, therapeutic vaccines break immunotolerance

mAb name	Trade name in the USA	Trade name in Europe	Used to treat	Nature of mAb/ produced in	Target molecule	FDA-approved in	EMA approved in
Rituximab	Rituxan	Mabthera	Non-Hodgkin lymphoma Rheumatoid arthritis (EU)	Chimeric/ CHO	CD20	1997	Jan 1998
Trastuzumab	Herceptin	Herceptin	Breast cancer	Humanised/ CHO	HER2	1998	May 2000
Gemtuzumab ozogamicin	Mylotarg	Mylotarg Gemtuzumab	Acute myelogenous leukemia	Humanised/ bacteria	CD33	2000	Sep 2007 neg. opinion by EMA!
Alemtuzumab	Campath	MabCampath	Chronic lymphocytic leukemia	Humanised/ CHO	CD52	2001	Mar 2001
Ibritumomab tiuxetan	Zevalin	Zevalin	Non-Hodgkin lymphoma	Murine/ CHO	CD20	2002	Sep 2003
ITositumomab	Bexxar	Tositumomab	Non-Hodgkin lymphoma	Murine/ mammalian cells	CD20	2003	EU, Orphan Drug designation
Cetuximab	Erbix	Erbix	Colorectal cancer Head & neck cancer	Chimeric/ SP2/0	EGF-R	2004 2006	2004
Bevacizumab	Avastin	Avastin	Colorectal cancer Non-small cell lung cancer Advanced breast cancer	Humanised/ CHO	VEGF	2004 2006 2008	2005
Panitumumab	Vectibix	Vectibix	Colorectal cancer	Human/ CHO	Competitive antagonist to EGF-R	2006	Sep 2007, conditional approval

Table 1: Monoclonal antibodies (mAb) approved by the FDA and/or EMA used to treat cancers

According to references 10 and 11, modified.

1: CHO = Chinese Hamster Ovary cells; 2: HER2 = Human Epidermal Growth Factor Receptor 2; 3: EGF-R = Epidermal Growth Factor Receptor, 4: Vascular Endothelial Growth Factor



VIENNA
SCHOOL OF
CLINICAL
RESEARCH

Vienna School of Clinical Research

BUILDING BRIDGES THROUGH TRAINING AND EDUCATION

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

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



VIENNA
SCHOOL OF
CLINICAL
RESEARCH

Vienna School of Clinical Research
Koelblgasse 10, A-1030 Vienna
Tel: +43 (0)1 7134051-0
Fax: +43 (0)1 7134051-99
Email: vscr@vscr.at
Web: www.vscr.at

Upcoming Courses in Vienna

07 – 11 Sept 2009	Systematic Reviews to Support Reimbursement Decisions and Evidence Based Medicine
11 – 16 Oct 2009	Health Outcomes Research: Pharmacoeconomics, the Economic Evaluation of Health Care
19 – 21 Oct 2009	Advanced Good Clinical Practice
29 Nov – 04 Dec 2009	Health Outcomes Research: Drug Pricing, Reimbursement Policy
07 – 11 Dec 2009	Publication Masterclass: How to Publish Abstracts, Posters, Review Articles, Observational Studies and Case Studies

and should be designed to avoid “wanted” immunogenicity but may result in “unwanted” immunity (15). From Table 1, few therapeutic monoclonal antibodies are humanised or human in origin; chimeric or murine antibodies are of major concern in evoking unwanted immunogenicity due to their allogeneic origin. There are obvious difficulties in determining potential immunogenicity of human mAbs during non-clinical drug development in non-human species. Brennan and Dougan (2005, 16) provide a comprehensive summary of non-clinical safety evaluation issues for novel vaccines and adjuvants and also provide recommendations on strategies to minimise potential concerns.

In Europe, there is current regulatory guidance on adjuvant use in vaccines for human use with respect to quality, non-clinical, pharmacokinetics and clinical (though not for therapeutic vaccines) development (17). It is not comprehensive and does not address several additional key issues, including haptens, antigens or excipients such as

Mineral salts, e.g.

- Aluminum hydroxide
- Aluminum or calcium phosphate gels

Oil emulsions and surfactant-based formulations, e.g.

- MF59 (microfluidised detergent stabilised oil-in-water emulsion)
- QS21 (purified saponin)
- AS02 [SBAS2] (oil-in-water emulsion + monophosphoryl lipid A (MPL) + QS-21)
- Montanide ISA-51 and ISA-720, (stabilised water-in-oil emulsion)

Particulate adjuvants, e.g. virosomes (unilamellar liposomal vehicles incorporating influenza haemagglutinin)

- AS04 [SBAS4] Al salt with monophosphoryl lipid A (MPL)
- ISCOMS (structured complex of saponins and lipids)
- polylactide co-glycolide (PLG)

Microbial derivatives (natural and synthetic), e.g.

- Monophosphoryl lipid A (MPL),
- Detox (MPL + M. Phlei cell wall skeleton)
- AGP [RC-529] (synthetic acylated monosaccharide)
- DC-Chol (lipoidal immunostimulators able to self-organise into liposomes)
- OM-174 (lipid A derivative)
- CpG motifs (synthetic oligonucleotides containing immunostimulatory CpG motifs)
- modified LT (Heat Labile toxin) and CT (Cholera Toxin, genetically modified bacterial toxins to provide non-toxic adjuvant effects)

Endogenous human immunomodulators, e.g.

- hGM-CSF or hIL-12 (cytokines that can be administered either as protein or plasmid encoded)
- Immudaptin (C3d tandem array)

Inert vehicles, such as gold particles

Human Serum Albumin (HSA), which is often used as a stabiliser.

Box 5: Adjuvants in clinical use

According to (17).

- Enhance / augment immune response
- Mount high titers of antibodies
- Influence kinetics of antibody production
- Provide depot effect for longer bioavailability
- Modulate Th1-/Th2-type balance
- Induce cytokines
- Modulate levels of cytokines
- Modulate / influence the antigen presentation route
- Directly interact with / stimulate Toll-Like-Receptors (TLR)
- Support tolerance induction mechanism

Box 6: Anticipated prominent effects / mechanism of action of adjuvants

Conclusion

The development of preventive vaccines reaches back more than 220

years, and it was Edward Jenner who coined the term “vaccination”. In contrast, therapeutic vaccines have only been developed in the last twenty-five years, the breakthrough coming with the development of monoclonal antibody technology, for which Georg Köhler and Cesar Milstein were awarded the Nobel Prize for Medicine in 1984.

Preventive vaccines are aimed at eliciting effective, protective immunity to pathogenic agents in non-infected individuals, whilst therapeutic vaccines are aimed at breaking immunotolerance in patients with a disease, usually of autoimmune, allergic, oncological or infectious origin. Both vaccine types require adjuvants, designed to achieve and to augment the desired immunogenicity or induce selective and antigen-specific tolerance induction. This overall aim is the elimination of disease or a clinically relevant alleviation in symptoms and signs.

Novel manufacturing approaches for preventive and therapeutic vaccines, in combination with a steadily growing family of adjuvants and a rapidly expanding group of advanced therapy medicinal products, will result in growing challenges to determine optimal quality, safety and efficacy profiles in alleviating a number of currently untreatable diseases.

References

- 1)** WHO fact sheet 288: Immunization against diseases of public health importance.
- 2)** WHO Vaccine-preventable diseases: monitoring system. 2007 Global Summary.
- 3)** Van der Zeist, B. 2008. Vaccines and global stability: achievements and challenges. *Exp Rev Vaccines*, 7: 1457-1460.
- 4)** Nakahara, W. The filterable cells of Rous Chicken Sarcoma and the question of the causative agent. *Science*, 64 (1658): 362-363, 1926.
- 5)** zur Hausen, H. Papillomaviruses in the causation of human cancers: a brief historical account. *Virology*, 20 (384): 260-265, 2009.
- 6)** Harandi, A.M., Davie, G., Olesen, F. 2009. Vaccine adjuvants: scientific challenges and strategic initiatives. *Exp Rev Vaccines*, 8: 293-298.
- 7)** Report 2008: Medicines in Development, Biotechnology, <http://www.phrma.org/files/Biotech%202008.pdf>
- 8)** Report 2008: Medicines in the Development of Cancer, www.phrma.org/files/meds_in_dev/Cancer2008.pdf
- 9)** Feldmann, M., Ravinder, N.M. 2003. TNF defined as a therapeutic target for rheumatoid arthritis and other autoimmune diseases. *Nature Med* 9: 1245-1250
- 10)** American Cancer Society, http://www.cancer.org/docroot/ETO/content/ETO_1_4X_Monoclonal_Antibody_Therapy_Passive_Immunotherapy.asp
- 11)** EPAR/EMA site: <http://www.emea.europa.eu/htms/human/epar/t.htm>
- 12)** Harber, M., Sundstedt, A., Wraith, D. 2000. The role of cytokines in immunological tolerance: potential for therapy. *Expert Reviews in Mol Med*. 27 November 2000, (00)00214-3a.pdf, ISSN 1462-3994.
- 13)** Nishimura, T., Iwakabe, K., Sekimoto, M., Ohmi, Y., Yahata, T., Nakui, M., Sato, T., Habu, S., Tashiro, H., Sato, M., Ohta, A. 1999. Distinct role of antigen-specific T helper type 1 (Th1) and Th2 cells in tumor eradication in vivo., *J Exp Med* 190: 617-627.
- 14)** Forsthuber, T.G., Ji, N. 2007. Quo vadis Th1 and Th2 cells in autoimmunity and infectious diseases: Th17 cells, the new kid on the block. *Expert Rev. Clin Immunol*. 3: 251-254.
- 15)** Hess, R.D., Russmann, D. 2009. Understanding immunogenicity responses. *Pharmaceutical Technology Europe*, volume 21, issue 2, Feb 2009.
- 16)** Brennan, F.R., Dougan, G. 2005. Non-clinical safety evaluation of novel vaccines and adjuvants: new products, new strategies. *Vaccine* 23: 3210-3222, 2005.
- 17)** EMEA/CHMP/VEG/13471/2004: Guideline on adjuvants in vaccines for human use. Jan, 2005.

Acknowledgement

The authors gratefully acknowledge helpful suggestions and critical reading of the manuscript by Drs Ravi Harapanhalli, Parexel Consulting, USA and Dieter Russmann, PAREXEL Consulting, Freiburg, Germany.

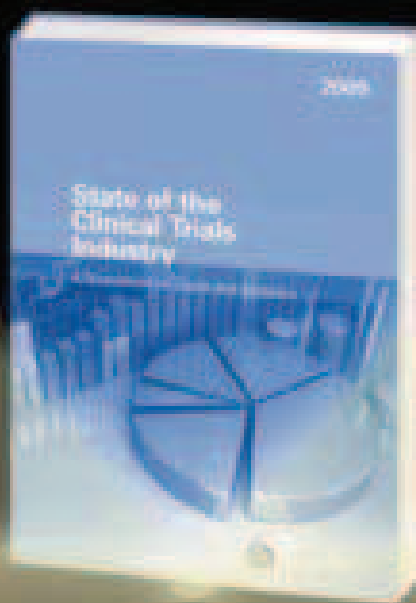


Ralf D. Hess, Principal Consultant, PAREXEL Consulting, has over 12 years of experience in the biopharmaceutical and medical device industry, including serving as Chief Scientific Officer for HISS Diagnostics GmbH, prior to joining PAREXEL. Dr. Hess is actively involved in numerous industry and scientific organizations and presents and publishes widely on topics including medical microbiology with a focus on virology and epidemiology, and emerging pathogens. Dr. Hess holds a Ph.D. and Masters in Biology from the University of Freiburg.



Partha Ghosh, Director, PAREXEL Consulting leads the consultancy's European Early Stage Development practice, focused on developing innovative and efficient solutions for clients to help them effectively address early stage challenges in pharmaceutical development. Prior to joining PAREXEL, Dr. Ghosh served for ten years as a clinician in the NHS specializing in ophthalmology with sub-specialty experience in medical retina, corneal disease and glaucoma. He also worked for several years as a management consultant in healthcare IT, clinical redesign, performance improvement and financial recovery projects and also has senior management experience at Clinical Operations Director level in private healthcare.

The only book you **NEED** this year.



Get the proprietary data you rely on.

NOW AVAILABLE



**Purchase your copy now for only \$699
and receive the 2008 edition FREE*!**

Visit <http://store.centerwatch.com>.

Reference code 7694. Offer ends July 31, 2009.

*While supplies last.





Malaria Vaccine Candidates - an overview

Introduction

Malaria kills over one million people each year, most of whom are children under five, and 90% of whom live in Africa, south of the Sahara. Malaria is responsible for one out of every four childhood deaths in Africa. Globally, there are over 300 million cases of the disease each year. The control of malaria has predominantly focused on pharmaceutical therapies and complementary methods such as mosquito nets, health education etc. The problems with the currently available pharmaceutical therapies include costs, availability, adverse effects and contraindications, inconvenience and compliance. Many of these would be reduced or eliminated entirely if an effective ($\geq 85-90\%$) vaccine was developed. It is clear that new methods of prevention are required, as the prevalence of malaria is still high globally, with worrying mortality and morbidity statistics.

Since the epidemiology of malaria varies enormously across the globe, it may be necessary to adopt different vaccine development strategies to target the different populations. A Type 1 vaccine is suggested for those exposed mostly to *Plasmodium falciparum*

malaria in sub-Saharan Africa, resulting in a reduction in the numbers of cases of severe malaria and deaths in infants and children exposed to high transmission rates. The Type 2 vaccine would be a 'traveller's vaccine', targeting individuals with no previous exposure.

Vaccine development so far...

Looking at the malaria parasite life cycle (fig 1), we can see that there are various areas that can potentially be targeted by vaccines. More than 30 vaccines are currently undergoing research all over the world, with an emphasis on *P. falciparum* (because of its high mortality and the ease of carrying out in vitro/in vivo studies). Different approaches are being employed; including surface expression of the antigen, inhibitory effects of specific antibodies on the life cycle and the protective effects through immunisation or passive transfer of antibodies between an immune and a non-immune host. The earliest vaccines attempted to use the parasitic circumsporozoite (CS) protein. This is the most dominant surface antigen of the initial pre-erythrocytic phase. However, problems were encountered due to low efficacy, reactogenicity and immunogenicity.

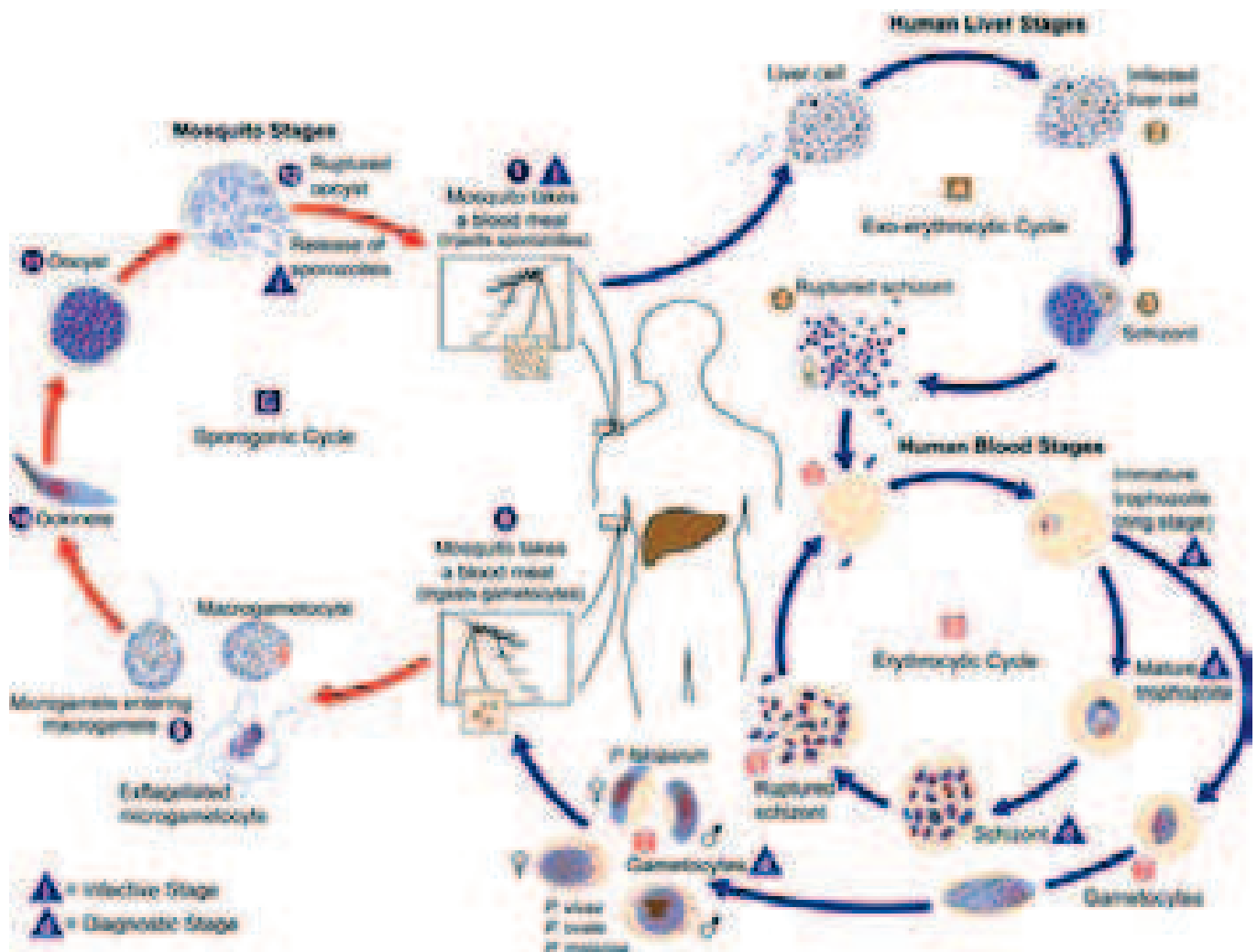


Figure 1: Malaria Parasite Life Cycle

Below is an overview of the main vaccine candidates that have managed to undergo human testing:

- **SPF66:** in 1987, Manuel Elkin Patarroyo, a Colombian pathologist, developed the first ever synthetic vaccine for malaria, SPF66. This vaccine was the first to undergo human clinical trials. It presents a combination of antigens from the sporozoite (using CS repeats) and merozoite parasites. In Phase I trials a 75 % efficacy rate was demonstrated and the vaccine appeared to be well tolerated by participants, with good immunogenicity. Results from Phase IIb and III trials however were discouraging, with the efficacy falling to between 38.8 % and 60.2 %. In a Tanzanian study (1993), SPF66 was found to have a 31 % protective efficacy in an area of intensive malaria transmission, in children aged between one and five years old, after a year's follow up.

Much more discouraging results were to be obtained in a 547-participant study in Gambia. In a randomised, double-blind, placebo-controlled trial of SPF66 against clinical *Plasmodium falciparum* malaria in Gambian infants, no differences in mortality or in health centre admissions were found between the two parallel study groups. Despite the relatively long trial periods and the number of studies carried out, it is still not known how the SPF66 vaccine confers immunity; it therefore remains an unlikely solution to malaria.

- **CSP:** the CSP was the next vaccine developed that initially appeared promising enough to undergo trials. It is also based on the circumsporozoite protein, but additionally has the recombinant (Asn-Ala-Pro15Asn-Val-Asp-Pro)2-Leu-Arg(R32LR) protein covalently bound to a purified *Pseudomonas aeruginosa* toxin (A9). However a Kenyan study concluded that CSP vaccine-induced ant sporozoite antibody is not protective in those inoculated. The study group had an 82 % incidence of parasitaemia whilst the control group had an 89 % incidence. Contrary to study expectations, no increase in T-lymphocyte response was demonstrated either.

- **[NANP]19-5.1:** in 1995, a clinical trial with the *P. falciparum* vaccine [NANP]19-5.1 yielded promising results. [NANP]19-5.1 is a recombinant *Plasmodium falciparum* vaccine consisting of 19 repeats of the sporozoite surface protein [NANP] and the schizont export antigen 5.1. Of the 194 Nigerian schoolchildren vaccinated, none developed symptomatic malaria in the 12-week follow up period, and only eight failed to have higher levels of antibody present. However, this vaccine candidate is limited by the fact that it contains no immunodominant T-cell epitopes. In its current form, the vaccine is only 20 % peptide and has limited immunogenicity. The use of recombinant IL-2 adjuvant in conjunction with this vaccine has proven to be potentially successful.

- **NYVAC-PF7:** the NYVAC-PF7 multistage vaccine incorporated seven *P. falciparum* antigenic genes from a variety of stages during the life cycle. CSP and sporozoite surface protein 2 (called PFSSP2)

were derived from the sporozoite phase. The liver stage antigen 1 (LSA1), three from the erythrocytic stage (merozoite surface protein 1, serine repeat antigen and AMA-1) and one sexual stage antigen (the 25-kDa Pfs25) were included. Initial investigations in Rhesus monkeys produced encouraging results: four out of the seven antigens produced specific antibody responses (CSP, PfSSP2, MSP1 and Pfs25). Human safety, immunogenicity, and efficacy Phase I/IIa clinical trials (USA, 1998) demonstrated cellular immune responses in over 90 % of the participants with, however, very poor antibody responses. Despite this, following administration of the vaccine some candidates had complete protection when challenged with *P. falciparum*. This result has warranted ongoing trials.

- **RTS,S:** the GlaxoSmithKline (GSK) recombinant vaccine candidate RTS,S is the first malaria vaccine to demonstrate sufficiently promising safety and significant efficacy to warrant Phase III testing and is the leading candidate in the effort by the PATH Malaria Vaccine Initiative (MVI) to develop a malaria vaccine. In Phase II studies, RTS,S demonstrated a 53 % reduction in malaria episodes over an eight-month follow-up period, and it has a promising safety and tolerability profile when compared to other infant vaccines. The vaccine has been undergoing clinical research for more than ten years in Africa. In 2004 and 2007, the first and second (respectively) proof-of-concept studies were conducted in Africa.

The RTS,S Recombinant Vaccine candidate

This vaccine candidate deserves special mention as it is the world's most promising, and the first to show convincingly that it can protect children against infection and clinical disease caused by *P. falciparum*. The RTS,S malaria vaccine was created in 1987. Its early development was undertaken by GSK Biologicals, the vaccine division of GSK, in association with the Walter Reed Army Institute of Research (WRAIR). In January 2001, GSK and the MVI, with the support of the Bill and Melinda Gates Foundation, agreed to develop the vaccine for infants and young children. The geographic focus was on sub-Saharan Africa. The RTS,S vaccine candidate is a recombinant protein that fuses a part of the *P. falciparum* circumsporozoite (CS) protein with the hepatitis B surface antigen. Combined with a proprietary GSK adjuvant system, RTS,S induces the production of antibodies and T-cells that are believed to diminish the capacity of the malaria parasite to infect, survive, and develop in the human liver. The RTS,S vaccine is also designed to protect against hepatitis B.

In 1992, clinical evaluation of the RTS,S/AS vaccine commenced in Belgium and the US in adults. In 1995 the first clinical trials began in Africa (Gambia and Kenya); and in 1997 a key proof-of-concept (PoC) study in the US and Belgium demonstrated 100 % protection in six of seven volunteers¹. Encouraging results were also obtained from another Key PoC study in Gambia (2001) in 306 semi-immune men. In this study, it was concluded that RTS,S/AS02 was a safe,

RTS,S Key Milestones

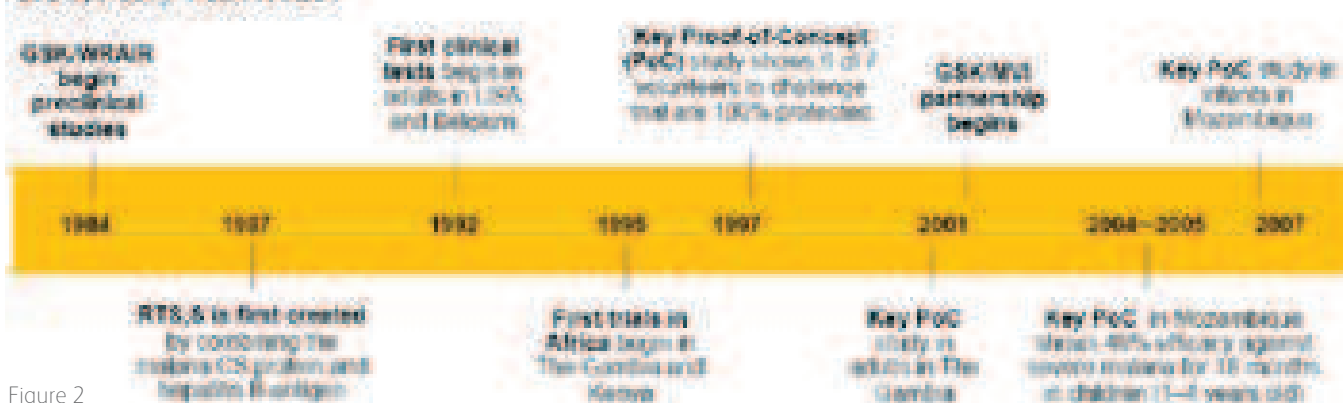


Figure 2

Clinical Trials in Russia?



Synergy Research Group

immunogenic vaccine that showed significant protection against natural *P. falciparum* infection².

Thereafter, results of a large double-blind, Phase IIb, randomised, controlled, RTS,S evaluation trial (2004) in southern Mozambique demonstrated the RTS,S vaccine as the most potent vaccine to date. During an 18-month period, in around 222 children aged 1-4 years, there was a 35 % reduction in the incidence of malaria, as well as a 49 % reduction severe malaria over an 18-month period. The results of this study were published in The Lancet medical journal in 2004 and 2005³.

Following the successful 2004 clinical trial, the RTS,S vaccine underwent further evaluation in other African countries. Mozambique, Tanzania, Gabon, Ghana, and Kenya all came on board in further testing of different formulations, dosing and dosing schedules of the vaccine candidate.

In November 2007, data from a Phase I/IIb, Key PoC Mozambican study showed that RTS,S reduced infection by 65.9 % over three months of follow-up, after a full vaccination course in 214 infants⁴. The vaccine also reduced the risk of clinical malaria by 35.5 % over a six-month period following the first dose. The safety and tolerability profile was shown to be similar to that of the standard Expanded Program of Immunisation (EPI) vaccines commonly given to infants, including compatible pain and swelling. This is encouraging; as such a vaccine could easily be part of regular infant immunisation programmes without special attention being required. The vaccine could be easily administered with minimal extra training for vaccination staff. This trial was the first proof-of-concept in infants of any malaria vaccine candidate.

In another single-centre, double-blind, controlled Phase IIb study (Bagamoyo, Tanzania - published in December 2008 in the New England Journal of Medicine), RTS,S/AS02D showed a promising safety profile, reduced incidence of malaria and no interference with immunologic responses to co-administration with other Extended Programme on Immunisation (EPI) vaccines⁵. 340 infants were enrolled. At least one serious adverse event was reported in 31 of 170 infants who received the RTS,S/AS02D vaccine, and in 42 of 170 infants who received the hepatitis B. The results showed the non-inferiority of the RTS,S/AS02D vaccine in terms of antibody responses to EPI antigens. One month after vaccination, 98.6 % of infants receiving the RTS,S/AS02D vaccine had seropositive titers for anticircumsporozoite antibodies on enzyme-linked immunosorbent assay (ELISA). During the six-month period after the third dose of vaccine, the efficacy of the RTS,S/AS02D vaccine against first infection with *P. falciparum* malaria was 65.2 %.

Also published at the same time were results from a Phase IIb study in Kilifi, Kenya, and Korogwe, Tanzania that evaluated the efficacy of RTS,S given with a more immunogenic adjuvant system (AS01E), in 5- to 17-month-old children⁶. A total of 894 children were randomly assigned to receive either the RTS,S/AS01E vaccine or the control (rabies) vaccine. All 894 children were included in the intention-to-treat analysis, which showed an unadjusted efficacy rate of 49 %. There were fewer serious adverse events among recipients of RTS,S/AS01E, and this reduction was not only due to a difference in the number of admissions directly attributable to malaria. The study concluded that RTS,S/AS01E shows good promise as a candidate malaria vaccine.

The positive results obtained from the Phase I/II studies set the stage for Phase III testing. A multinational, multicentre Phase III trial is planned to commence in 2009, aiming to fully determine the efficacy of the vaccine. This study is set to be the largest ever vaccine trial in Africa.

Looking into the future..

The most recent advances in the field of sub-unit vaccine development include the use of DNA vaccines. DNA vaccination was introduced in 1990 by a study that demonstrated the induction of protein expression upon direct intramuscular injection of plasmid DNA in myocytes. DNA vaccines are new types of sub-unit vaccines allowing protein expression in mammalian cells after introduction of plasmid or recombinant viral vectors encoding the selected protective antigen. These vaccines induce strong humoral and cellular immunity and have the potential to increase immunogenicity through modifications of the vector or incorporation of adjuvant-like cytokine genes. Successful vaccines should be able to induce strong, long-lasting immune responses which are effective against different strains of the same pathogen. This new vaccination technology has already been applied to bacterial and viral pathogens. However, parasite infections, unlike most viral and bacterial infections, tend to be chronic and associated with immunodepression or inappropriate immune responses. Complex life cycles, antigenic variation and other immune evasion mechanisms also complicate the development of vaccines against malaria parasites. However, with recombinant DNA technology and the versatility of DNA vaccination, it is now possible to take rational parasite specific strategies to vaccine design and overcome these obstacles. Improving DNA vaccine efficacy against parasitic disease can be achieved by: prime-boost immunisations, genetic adjuvants, multivalent vaccines or codon optimisation. Scientists and the medical profession are applying these strategies to vaccine research, with at least one DNA vaccine having started human testing.

As mentioned above, the RTS,S vaccine candidate is the most advanced to date. The launch of the Phase III trial of RTS,S marks a major research milestone after more than 20 years of research and development. This trial will include 11 sites in Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and Tanzania, as required local and national reviews are obtained. Together, the 11 sites will eventually enrol up to 16,000 children and infants, making this the largest malaria vaccine trial to date. If successful in Phase III trials, the registration of the vaccine is envisioned for 2012. This vaccine is expected to be an innovative approach to combat malaria as the first ever registered malaria vaccine. The widespread use of this product would in turn result in a global reduction in the incidence, mortality and morbidity of malaria. ■

References

1. Stoute JA, Slaoui M, Heppner DG, Momin P, Kester KE, Desmons P, Welde BT, Garcon N, Krzych U, Marchand M, Ballou WR, Cohen JD for the RTS,S Malaria Vaccine Evaluation Group, 1997. A preliminary evaluation of a recombinant circumsporozoite protein vaccine against *Plasmodium falciparum* malaria. *N Engl J Med* 336: 86-91
2. Bojang KA, Milligan PJ, Pinder M, et al. Efficacy of RTS,S/AS02 malaria vaccine against *Plasmodium falciparum* infection in semi-immune adult men in The Gambia: a randomised trial. *Lancet* 2001;358:1927-1934.
3. Alonso PL, Sacarlal J, Aponte JJ, et al. Efficacy of the RTS,S/AS02A vaccine against *Plasmodium falciparum* infection and disease in young African children: randomised controlled trial. *Lancet* 2004;364:1411-1420.
4. Aponte JJ, Aide P, Renom M, et al. Safety of the RTS,S/AS02D candidate malaria vaccine in infants living in a highly endemic area of Mozambique: a double blind randomised controlled phase I/IIb trial. *Lancet* 2007;370:1543-1551.
5. Abdulla S et al. Safety and immunogenicity of RTS,S/AS02D malaria vaccine in infants. *N Engl J Med* 2008 Dec 11; 359:2533.
6. Bejon P et al. Efficacy of RTS,S/AS01E vaccine against malaria in children 5 to 17 months of age. *N Engl J Med* 2008 Dec 11; 359:2521.



Dr. Sheperd Moyo has worked for 4 years in clinical practice; as well as for over 2 years in clinical trials (UK and South Africa). He currently works as a medical advisor for ONQ Research Pty Ltd., a leading clinical research organisation in South Africa.
Email: sheperdm@onqa.co.za, **Website:** www.onqa.co.za

Diagnosis of Brucellosis at the present stage & Pathogenesis grounds of immunity-modulated therapy of brucellosis.

Part A

Diagnosis of Brucellosis at the present stage:

One of the main conditions of successful treatment in any disease is its correct and timely diagnosis. Early diagnosis in brucellosis has great epidemiologic value and allows one to carry out antiepidemic actions against the infection in a timely manner [1].

Brucellosis diagnosis is carried out on clinical and epidemiological data, and proved by positive laboratory results. Our control demonstrates the preservation of the main and most typical attributes, though their frequency and degree of expressiveness have greatly changed in the modern brucellosis clinic, aggravated by *Brucella melitensis*. Most common are mild (37.2 per cent) and medium severity (37.2 per cent) of brucellosis. Lesions of osteoarthricular system in the form of stable and expressed polyarthralgias, monoarthritis, shoulder blade and humeral peri-arthritis, spondylitis, bursitis etc. are most common in the subacute brucellosis clinic.

One of the reasons for error and untimely diagnostics is clinical changes of acute and subacute brucellosis – increasing of light and not so bright forms of the disease. For example, in 1/3 of cases where patients were diagnosed on admission with acute brucellosis, the diagnosis was found to be incorrect. They were later diagnosed as pneumonia, bronchitis and acute respiratory infections in the first days of the disease.

Another inopportune factor concerning diagnostics arises because of the late date of hospitalization. For example, in the first week of disease only 11.4 per cent of patients were hospitalized; in the second, 12.5 per cent; in the third, 14.4 per cent; in the fourth, 29.5 per cent; in the second month of disease, 25.7 per cent; and in the third month, 12.6 per cent of patients. It is crucial to note that untimely diagnosis of brucellosis has a very negative influence on the effectiveness of medical treatment.

The essential method for timely and right diagnosis has involved the collection of detailed epidemiological data: living in an endemic seat of brucellosis, looking after domestic animals, eating raw milk and dairy products etc. It has been determined that this disease had a professional character (i.e. the infection is usually transmitted by direct contact with animals, raw meat and animal products; shepherds, dairymaids, veterinary workers etc) only in 10.8 per cent of patients with acute and subacute, and in 40.1 per cent with chronic brucellosis. Non-professional infection was prevalent among the patients with acute – 52.5 per cent and subacute – 56.6 per cent.

In connection with polymorphism of clinical displays of brucellosis, laboratory methods of research – namely bacteriological, serological, dermal-allergic test and polymerase chain reaction (PCR) – have important diagnostic value.

The bacteriological method of diagnostics has absolute

diagnostic value. However, haemoculture is exuded only in 15.4 per cent of patients with acute and subacute brucellosis (according to our research data). The efficiency of this method depends on many factors; quality of nutrient medium, dates and correct methods of transportation of pathological materials, peculiarities of micro- and macro-organism. The date of bacteriological research averages 30-45 days.

One of the up-to-date, specific and highly sensitive methods of diagnostics of brucellosis is PCR, which allows confirmation within one working day of the presence of brucellosis in investigated material. We determined that the PCR sensitivity is 93.9 per cent and specificity is equal to 100 per cent. However, test systems for PCR are very expensive and cannot be widely used in practice, therefore serological reactions are the most commonly available method of laboratory diagnostics of brucellosis, allowing one to follow the dynamic of antibodies' titer and the phase of the infection process. It is necessary to remember that specific antibodies in small titers can be the result of «unprofessional» immunization and have non-specific character because of the presence of common antigens with other micro-organisms. Negative results of serological reactions cannot guarantee in all cases that there is an absence of brucellosis in the clinic's epidemiological data. We determined that specific antibody titers can influence the result of disease. So, the process of chronization, according to our research, is observed in 44.4 per cent of patients with acute brucellosis, and in 52.2 per cent of patients with subacute brucellosis. In spite of all this, high titers of specific antibodies were observed in 62.1 per cent of patients with auspicious results. On the other hand, chronization of brucellosis was registered in 56.6 per cent of patients with negative results from serological reactions. It is possible that a deficiency of intensity of the humoral chain of immunity leads to incomplete elimination of the activator from the organism, causing chronic illness.

Thus, total and purposeful analysis of clinical displays and epidemiological data, wide and early use of serological methods of research in each suspicious case in brucellosis, and constant watchfulness of doctors concerning brucellosis provides a real opportunity for the up-to-date and correct diagnosis of brucellosis.

Part B

Pathogenesis grounds of immunity-modulated therapy of brucellosis

In the pathogenesis of brucellosis, according to the results of our complex immunological research and literature data [1,2], side by side with general-known facts [bacteraemia, toxæmia, allergic], of great importance is the discovery of immunological breaks which arise at various stages of illness development. Clearing up

the role of immunological mechanisms in the development of the pathological brucellosis process has great value for the foundation of immunological therapy.

Nowadays chronic recurrence of illness is considered as the second immunological deficiency [3]. Complex investigations show that within the development of brucellosis, there are formed numerous inter-communicated immunological breaks the character and degree of which are connected with the clinical form and course of a disease, the strength and extensiveness of organ affection, and the degree of allergic reorganizations in the organism. The most expressed quantitative and functional changes of cell and humoral immunity are observed in active forms of brucellosis, especially in a heavy occurrence of illness. Immunological breaks, typical of brucellosis, are undoubtedly connected with long intra-cell preservation of an activator in the organism, so there is a constant probability of activation of the infection process.

Incompleteness of phagocytosis, connected with deficiency of macrophages ferment system are caused by long intra-cell presentation of an activator in the organism. Not all of Brucellae are destructed, and what is more, the conditions are created for their reproduction and spreading all over the organism. Constant antigenemia breaks a final differentiation of lymphocytes, which leads to an expressed and stable quantity deficit of T-lymphocytes and their sub-population. Production of the specific antibodies leads to the formation of circulating immune complexes, which influence first of all the endothelium of blood vessels.

It has been determined by us that a definite role in the pathogenesis of brucellosis is played by cytokines: tumor necrosis factor, interleukin-2, interleukin-4, interleukin-6, interleukin-10, lactoferrin, α - and γ - interferons whose content is closely connected

with the degree of danger and the phase of process development.

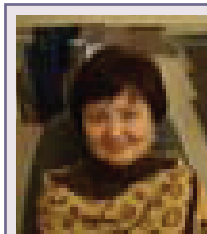
Thus, the development of immunopathologic reactions in brucellosis is connected with forming the second immunological deficiency of the immune T-system.

Taking into consideration the essential role of immune mechanisms in brucellosis development, their depth and many different aspects, the pathogenetically proved approach is the use of medical remedies, having a wide spectrum of influence on various chains of immunopathogenesis.

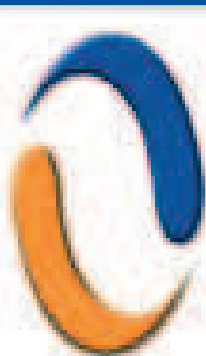
The up-to-date level of clinical immunology allows us to study in detail and to estimate the role of numerous immunological breaks for each concrete brucellosis patient and to approach with validity the treatment of a given illness, i.e. differential application of non-specific immunity-modulated therapy with the influence on the concrete chains of immunity.

References – Part A 1. Lang R., Bani M. et al. *Brucellosis / International J. of Antimicrobial Agents*. 1995 – V.5. – P. 203-208. 2. Corbel M. J. *Brucellosis: an overview / Emerg. Infect Dis.* 1997. Apr-Jun., 3[2] – P. 213-221. 3. Kurmanova K. B., Duisenova A. K. *Brucellosis. Clinical Aspects*. - Almaty, 2002. - P.183-226.

References – Part B 1. Elberg. S. S. *Immunity to brucella infection / Medicine*. 1973. - Vol. 53. - P. 339-356. 2. Lang, R., Banai, M., Lishner, M. et al. *Brucellosis / International J. of Antimicrobial Agents*. - 1995 – V. 5. – P. 203-208. 3. Kurmanova K. B., Duisenova A. K. *Brucellosis. Clinical aspects*. - Almaty, 2002. - P. 23-37.



Sh. A. Kulzhanova MD, PhD. Position: Head of Department of International Cooperation, Astana Medical University, Executive Secretary of National Ethics Committee. I have been working in public health sector for many years. My research interest: bioethics, public health. International experience: I was PI for several projects with COHRED (Geneva), AHPSP (WHO), UNESCO.



8th Annual Partnerships in Clinical Trials Congress and Exhibition 2009

3-6 November 2009, World Trade Centre, Rotterdam, The Netherlands

Rare opportunity to hear
from Anatole Kaletsky,
Associate Editor, and
Principal Economic
Commentator,
The Times

CONFERENCE CHAIR:



John Sergeant, Author,
Broadcaster and Former BBC
Political Correspondent

KEYNOTE ECONOMIST



Anatole Kaletsky, Associate Editor,
and Principal Economic
Commentator, The Times

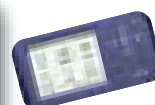
INSPIRING GUEST SPEAKER



Stephen Carver, Project
Management Specialist and Lecturer
at Cranfield University, One of
Europe's top business schools

PARTNERSHIPS IN CLINICAL TRIALS 2009 WILL DELIVER:

- Strategic and practical case studies of the industry's most successful clinical partnerships
- Expert analysis on the global economy (and the implications for Pharma)
- Comprehensive update of the changing service provider market
- Thorough industry analysis from large, medium and small Pharma/biotech companies
- Inspiring out-of-industry perspectives on how to partner for value and quality



Back by popular demand:
networking with 'Spotme' devices

www.ct-partnerships.com

To register:

Call: +44 (0) 20 7017 7481 Fax: +44 (0) 20 7017 7823

Email: registrations@informa-ls.com Web: www.ct-partnerships.com

Book before 4th September 2009 and save up to £300. Please quote CQ3004JCS

informa
life sciences formerly known as

Specialist courier and logistics solutions for your clinical trial needs challenges

Today's pharmaceutical companies, contract research organisations (CRO's) and drug distributors face ever increasing challenges in maintaining the stability and validity of their products in transit. With clinical trials being conducted in new markets and far reaching countries, the logistics involved in delivering time-critical and temperature controlled investigational medicinal products (IMP) within stability becomes even more challenging. Marken has risen to this challenge and developed a range of solutions to meet these challenges.

MARKEN'S TEMPERATURE CONTROLLED VEHICLES (TCV's) are capable of maintaining a range of temperatures during transit from -25°C up to +20°C through use of on-board refrigeration and air conditioning units which heat or chill the air in the insulated cargo compartment of the vehicle to the set temperature. Clinical trial medicines requiring to be kept between +2 and +8°C can be collected from the shipper, loaded into a pre-conditioned TCV and then driven directly to the consignee anywhere within the UK, western Europe, eastern Europe and as far a field as Russia. These custom built vehicles also have separate generators for use when the engine cannot be kept running, or fails. Marken's TCV's also have power leads with adapters for plugging into mains electrical power supplies during ferry crossings, when the driver is sleeping and other times when it is not possible to keep the vehicle's engine running. With on-board monitors and GPS tracking, the shipment can also be tracked in real time and the temperature results of the vehicle viewed at any time. An alarm will sound if the temperature goes out of range or there is a system failure. The system can also be set up to send an alert via text to any mobile phone, thus ensuring total control and peace of mind.

TEMPERATURE CONTROLLED AIRCRAFT CONTAINERS are capable of maintaining a range of temperatures from -20°C up to +20°C, making them ideal for bulk shipments of -20 oC. (Frozen), 2-8°C (Refrigerated) and +15 to +25°C (Controlled Ambient) IMP. These containers use a combination of dry ice bunkers - to chill the air, heating elements - to heat the air, and fans to circulate the conditioned air through the container at the required temperature.

Certain types of temperature controlled aircraft containers use only powerful air compressors and heating elements to chill or heat the air to the desired temperature. These containers ability to heat the internal air if the external air temperature is too cold and chill the air if the external air temperature is too warm, make them ideal for ensuring clinical trial medicines remain within the required temperature parameters all year round and especially when shipping from a cold origin to a hot destination country and vice-versa.

UNIQUE HYBRID TRANSPORT SYSTEM Marken has developed a unique hybrid transport system by collecting the bulk IMP supplies in a TCV, driving to the departure airport and then transferring the consignment into a pre-conditioned temperature controlled aircraft container for final loading onto the planned flight. QUALIFIED & VALIDATED disposable 'off-the-shelf' packaging systems are yet another packaging solution Marken can provide for maintaining temperature control of IMP during transit. PHASE CHANGE TECHNOLOGY has been harnessed with the invention of advanced re-useable passive temperature controlled

containers. QUALIFIED DRY ICE SHIPPER CARTONS are used extensively by the Marken to arrange the uplift of clinical trial patient blood samples from investigator sites around the world and transport back to central laboratories for diagnostic testing. As a matter of course Marken will monitor the transit very closely, and in the event delivery is not possible before this lifespan elapses, the specialist courier will arrange the transfer of the validated packaging to refrigerated storage within the customs/ airline bonded warehouse, and arrange either replenishment of the gel packs, or delivery in a TCV. Thus ensuring the integrity of the IMP temperature is not compromised. TEMPERATURE MONITORING DEVICES Marken can also provide a range of temperature monitoring devices which can be programmed to record the temperature during transit every set number of minutes. Marken has interface and software technology at the destination office which saves valuable days in the process.

MARKEN'S SOLUTION: A CASE STUDY

The following is a real-life case study showing how these solutions can be put together by a Marken to provide a tailored solution for the shipper.

The Scenario;

A CRO based in the United Kingdom, had a bulk consignment (14 drums @ 308Kgs) of a Phase II IMP to be transported to Kansas City, USA. The IMP must be kept between +2 and +8°C at all times. The shipper had no 2-8°C. Validated Packaging for this material. In addition, due to the quantity, value and manufacturing time of the tablets, the CRO's sponsor requested the shipment be split into 2 consignments and travel on separate vehicles and flights at all times to reduce the risk of loss of total consignment in the event of 'Force Majeure'.

Our Solution;

Marken arranged collection from the shipper in 2 separate TCV's set at, and pre-conditioned to, +5°C. The shipment was driven from the shipper's premises to Heathrow Airport, where it was loaded into 2 separate Refrigerated Aircraft Containers, which were also set at, and pre-conditioned to, +5°C. As there were no wide-bodied international flights from UK to Kansas City available, the specialist courier flew the 2 containers on 2 different flights into San Francisco, where the courier's San Francisco office ensured the containers were re-iced, re-charged and kept running at +5°C. Once cleared through customs and FDA, the shipment was driven from San Francisco to Kansas City in 2 separate TCV's at +5°C. The temperature monitors enclosed beside the IMP showed the consignment remained within the required +2 to +8°C temperature range during the entire transit.

Marken is one of the fastest growing specialized logistics and support services companies to the pharmaceutical industry, fulfilling a key role in all phases of research and drug development.

Having a global network of facilities, our services include the export of trial medication, vaccines and clinical trial material, cold-chain management, protocol support and regulatory advice, investigator liaison and biological sample movement on a global basis. Our objective is to ensure that we provide our customers with superior support services to provide a cost effective, flexible and streamlined process that will add value and facilitate accelerating the process of drug development.

Fundamental errors when working with central laboratories

Global centralised laboratory services – if global means that two or more continents are involved in a clinical trial - are now available for approximately fifteen (15) years. The first central laboratories were founded in North America some twenty years ago: a logical step in view of the vast size of this region covering the USA and Canada, a region with no major borders and with nationwide couriers already available at that time. In the mid 1990s, cross-border transportation in Western Europe was simplified by the creation of a European Union and this triggered the setup of central laboratories in Europe.

Since 1995 many centralised laboratories have been established to provide bi-continental (America-Europe) or more global central lab services; most have failed and only a few have survived and are today able to offer reliable and high-quality services.

Central laboratory services are complex, particularly due to the logistical tasks involved. A poor understanding of processes during the planning phase has the irrevocable consequence that sites may prepare their samples inappropriately, that samples may undergo unexpected delays during shipment and that lab results may not be available at the site for the next patient's visit. Sponsor companies (essentially pharma and biotech) generally make their service provider responsible for all such problems and are not aware that they could have done better during the selection process.

What is the major misunderstanding when using central laboratories?

My impression is that many sponsors still do not invest sufficient time in developing appropriate selection criteria to allow them to identify the ideal central lab. This may be due to the fact that the cost related to the laboratory portion of a clinical trial only amounts to 10 % (if only routine safety panels are needed) to 20 % (if more complex analytical methods and international logistics are required) of the overall study budget. Why invest too much time in laboratory selection if this portion of the study is considered to be marginal?

This approach seems to be widespread and to me is based on the fundamental error in thinking that all laboratories are essentially comparable with each other. Proof of this could be that only a very few sponsors take the time to visit the laboratory candidates before awarding their contracts.

Table 1 shows that sponsors should be looking for service providers able to provide all sub-services they need, and not only appropriate analytical support.

“Central laboratory services are complex, particularly due to the logistical tasks involved.”

How is this misunderstanding nurtured?

One major reason for this misunderstanding, i.e. that a central laboratory is just a laboratory, is also found in many of the publications describing the use of centralised lab service providers. Hence scientists at a sponsor willing to know more about the use of a central lab may read publications generally only describing analytical processes as well as quality aspects relating to the lab testing itself.

Such laboratory-oriented publications thoroughly evaluate operational and quality aspects with respect to a) requirements for appropriate lab facilities, b) equipment and reagents, c) qualification of the lab staff, d) quality control schemes and e) LIMS (laboratory information management systems).

If we go back again to Table 1 we will easily find out that all these items only refer to the first 1 or 2 sub-service types, i.e. they only refer to the analytical portion. But the analytical work – although very important - is only one more service type to be expected from central laboratories (1).

How to correct this fundamental error?

Table 1: Sub-services offered by “standard” laboratories and by central labs.

Type of Service	Standard reference lab	Central laboratory
Routine lab testing	✓	✓
Specialised methods, biomarkers	(✓)	✓
Dedicated project managers	-	✓
Cross-border shipping logistics	-	✓
Visit-specific kit building	-	✓
Frozen sample library	-	✓
Customised data formatting	-	✓
QA available for all processes	-	✓
Multi-lingual support	-	✓

Table 1

Selection criteria for choosing a central laboratory

- Are all tests done in-house and if so, daily?
- Are validated methods used and generic reagents avoided?
- How are samples identified?
- Is external accreditation available?
- Are project managers allocated to the study?
- Do they search for missing data and attend investigator meetings?
- Does a quality assurance unit supervise all processes and training?
- Are sampling kits and study specific instructions supplied to investigators?
- Are lab reports, data transfer and progress reports customised?



central lab services for clinical trials

competitiveness = unexpected

quality awareness = uncommon

flexibility = unlimited

why pay more elsewhere?



lab results you can trust



**Customized
central lab services with global reach
for
15 years: 1994 – 2009**



Competitive Services / Transparent Costs

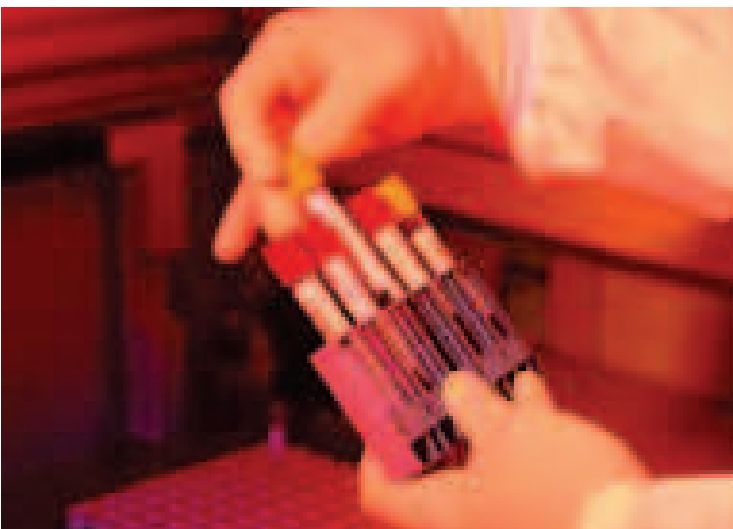
- over 15,000 samples/day in Europe: economies-of-scale
- since 1994, established infrastructure for global studies
- since 2005, global IT platform compliant with 21CFR11
- country-specific flat fees for transportation: no surprises
- **unless your budget is unlimited: why pay more elsewhere?**

Project Managers = key to INTERLAB's success

- project teams in USA and Germany
- dedicated scientists, many with a PhD degree
- experienced, reliable, flexible and pro-active

Range of Services - no one likes limits

- bio-analytical services
- assay development
- extended sample storage
- worldwide shipping
- visit-kits: automatic re-supplies
- small, regional studies; Phase I-II
- international trials; Phases II-IV
- one global QA system: ISO15189



INTERLAB
central lab services

EUROPE – ISRAEL – NORTH AND SOUTH AMERICA – SOUTH AFRICA – AUSTRALIA – ASIA
Head Office: Bayerstr. 53, D-80335 Munich, Germany
INFO-PHONE: +49 89 741 393 0 – E-MAIL: INFO@INTERLAB.DE
www.INTERLAB.de

Although some sponsor companies may rely on the expertise of their scientists when selecting a central laboratory, other sponsors have set up specific teams with the aim of standardising the selection process.

Such “outsourcing” teams may be located in the R&D or in the purchasing departments and generally develop complex RFIs (request for information questionnaires) in order to collect information from the service providers in a structured grid-format.

I do not intend to comment on the various options available, only to say that in view of the reduced number of global central laboratories (not more than ten) and the significant differences between them, I would recommend those people responsible for the lab selection to personally visit all (!) those ten or so central laboratories. One day per lab and limited travel expenses would deliver more reliable information than collecting information, the quality and truth of which may be very difficult to prove. A second step would include sending qualified auditors to a selection of those central labs.

Are there different types of centralised laboratories?

The author has described elsewhere the various types of central labs available and each sponsor should evaluate which should be the more appropriate for each study protocol (2). In view of the economic uncertainty, many sponsors are becoming more selective about the CROs (contract research organisations) and central labs they want to use to better capitalise on in-house competencies. Particularly in the central laboratory sector, with a limited number of global players and each one with very specific strengths, the limitation to only two or three “preferred providers” may turn out not to be the right path. The current financial world forces not only sponsors but also service providers to restructure their organisations (3). Unhealthy players have already closed down or will disappear. This should provide additional support for the above recommendation: only if you have personally visited all ten or so

global central labs can you be sure to have an alternative service provider if one of your preferred ones suddenly reduces its capabilities or, worst case, closes down.

“One day per lab and limited travel expenses would deliver more reliable information than collecting information, the quality and truth of which may be very difficult to prove. A second step would include sending qualified auditors to a selection of those central labs.”

How can the right central lab be identified?

This is a very difficult question and the basis for either future satisfaction or unhappiness.

There are a number of questions that can help in identifying the appropriate candidates (Table 2). But the answers should only be evaluated and balanced against each other if the respective laboratories have also been previously visited.

The standard question raised by a sponsor is: do you perform the tests ABC?

Most central laboratories will be able to say yes, even if they would need to set up and validate a new method. Interestingly, follow-up questions are generally forgotten:

- Are all tests done in-house? What if you have selected a central lab with a wonderful QA management system which then refers your blood samples to a third party with a lower quality awareness?
- Are all tests measured daily? If this issue is not raised, the contract may have been signed prematurely: if sites need their lab results soon after blood collection in order to re-evaluate their patients’ drug dosage it would be a major problem if the laboratory

selected only runs the specific method once every three or four weeks. The frequency of running a specific assay in the laboratory depends directly on the number of samples received. A small laboratory processing 50 or 100 samples a day may only receive 5 to 10 samples for a specific immunology method. Consequently, it would hardly be able to run this specialised method due to the high cost of instrumentation (up to US\$250,000) and reagents (US\$1,000 for a kit to test approx. 40 samples) in addition to the need for qualified technicians. Sponsors should therefore find out at an early stage if the laboratory to be chosen is able to perform the study-specific test panel with shortest delay.

What is the added-value of using centralised laboratories?

As mentioned above, it would not seem sufficient to simply find out if a central lab is able to comply with the analytical requirements of a study protocol. A central laboratory has many other tasks to reliably fulfil.

Table 1 shows the major differences between laboratories. Important questions should therefore include whether dedicated project managers would be allocated to the study, whether they would coordinate all activities and be the single contact for the sponsor, whether they would attend investigator meetings and there present the logistics involved with sample collection and transportation, whether they would write study-specific multi-lingual investigator manuals and shipping instructions, whether they are aware of IATA regulations and customs requirements.

TABLE 2: SELECTION CRITERIA

- are all tests required available routinely?
- or have samples to be referred to another lab?
- are all methods done on a daily basis?
- are in-house experts available?
- are all methods validated (SOPs available)?
- how are all samples identified? double entry?
- proven experience in international logistics?
- are non-generic reagents used?
- quality control and quality assurance in place?
- design of lab report flexible? in English?
- customised data management available?
- experienced project management in place?
- which languages are spoken?

Conclusions

Most drugs being evaluated in clinical trials require analytical laboratory work to prove their safety and efficacy. This is different from the past where laboratory data was mainly used for safety reasons only. Whereas "standard" laboratories in major hospitals or universities may be able to run methods for more specialised methods required in the study protocol, most local laboratories used by investigators are limited to offering routine lab testing.

In contrast to using a central laboratory, local laboratories use different methodologies and reference ranges, different units and languages, different analytical quality and staff training procedures. Such discrepancies related to the use of decentralised laboratories may jeopardise the outcome of multi-country studies. Language differences and also other ways of interpreting lab values, especially those outside the reference ranges, may further compound methodological differences.

Globally operating central laboratories have established uniform SOPs (standard operating procedures), IT platforms and QA standards in all regional lab facilities and hence are able to provide all lab data in a single data format using global reference ranges and units. Data uniformity and comparability is the basis for reliable statistical analyses.

Central laboratories provide a simple promise: perform high-quality analytical work centrally! This simple promise is not easily fulfilled. A number of potential challenges exist and must be taken into account during the setup of each individual study. To achieve their goal, central laboratories provide an added value if compared with "standard" laboratories. In order to obtain satisfactory results

from the central laboratory selected sponsors are expected to invest more time and effort in the selection process and to base their decisions not only on questionnaires but on personal visits and inspections. Preferred service providers selected some years ago may definitely not be the most appropriate candidates in today's changing environment. ■

References

1. H. Schulz, "Outsourcing Laboratory Testing for Clinical Research: Advantages for Pharma and Biotech Companies", *GOR Global Outsourcing Review Journal* (with Japanese summary), Vol. 5, No. 1, 27-30, 2003
2. H. Schulz, "Central Labs: Types, Distribution and Capabilities", *European Pharmaceutical Contractor Journal EPC*:114-120, Summer 2007
3. H. Schulz, "Financial crisis and its potential impact on clinical research –from the central laboratory perspective", *Journal for Clinical Studies*: 38-40, January 2009



Dr. Hermann Schulz held senior R&D positions in pharmaceutical industry (Merck&Co, Astra-Zeneca/ICI and Schwarz) during 12 years and was responsible for R&D in the cardiovascular area. As a visiting professor, Hermann Schulz is head lecturer for clinical pharmacology in the post-graduate course "Pharmaceutical Medicine" at the University Duisburg-Essen (formerly Witten-Herdecke) and also teaches at the University of Tuebingen. He was member of the Board of the German Society of Pharmaceutical Medicine for six years and is founding member of the International Association of Central Laboratories IACL based in London. Hermann Schulz has written more than 35 scientific publications and is invited as speaker to international conferences such as DIA or IIR.

Email: ceo.schulz@interlab.de





Powerful Web-based LIMS Supports Clinical Trial Expansion into Emerging Countries

Recruitment of subjects is a major bottleneck in many clinical studies causing problems to companies seeking regulatory approval for new products. However, with large populations eligible to participate in clinical studies, an ample supply of trained clinical investigators, and the opportunity to reduce trial costs by up to half compared to the U.S. or Western Europe, clinical trial activity is on the rise in many emerging markets including Eastern Europe, Latin America, Asia, and Africa. The expansion of clinical trials into these areas can present significant challenges due to the lack of infrastructure, inadequate quality standards and quality assurance awareness, transportation issues, and complicated customs procedures for shipping supplies and biological specimens.

Successful execution of a clinical trial in these emerging countries requires that the clinical trial specimen collection, handling, shipping, and testing processes are tightly managed despite these challenges. A flexible and feature rich Laboratory Information Management System (LIMS) can accommodate new investigator and specimen testing sites and will enable effective management of the kit supply chain, specimen collection, storage, testing, and laboratory result management. The LIMS must also support multiple languages in both the user interface screens and in reports.

Key characteristics of a clinical trial LIMS include:

Web based access & Scalable Design

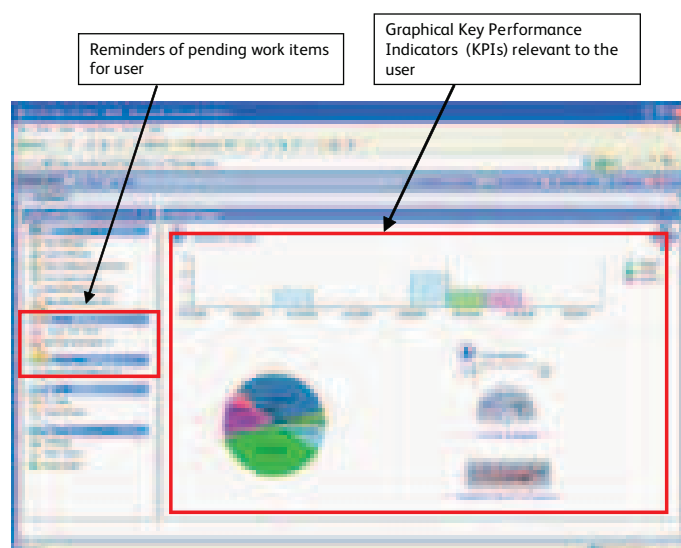
A true web-based clinical trial LIMS will provide secure, anytime, anywhere access to the system for authorized users, eliminating isolated pockets of information and enabling clinical trial laboratory operations to be managed at an enterprise level. An integrated clinical trial laboratory informatics system will use a common data base to enhance the visibility of information for all stakeholders. A web-based system will have no client side software installed allowing simple roll out to new users. Furthermore, there is no system management burden imposed when upgrades and new releases become available. If external users require access to additional functionality within the system, this can be achieved by simply changing their role or access definitions.

A modern web-based system can provide the advantages of a zero-install application operating within Internet Explorer while still providing the rich client features including a highly interactive GUI and the ability to interact with physical devices such as instruments, barcode scanners, and biometric devices. The web application architecture should function in low bandwidth scenarios and should be easily scalable taking advantage, for example, of the latest Microsoft® Windows server clustering capabilities to provide both load balancing and High Availability. As data throughput increases with additional trials being conducted across a greater number of investigator sites, the LIMS should easily accommodate the load by simply adding

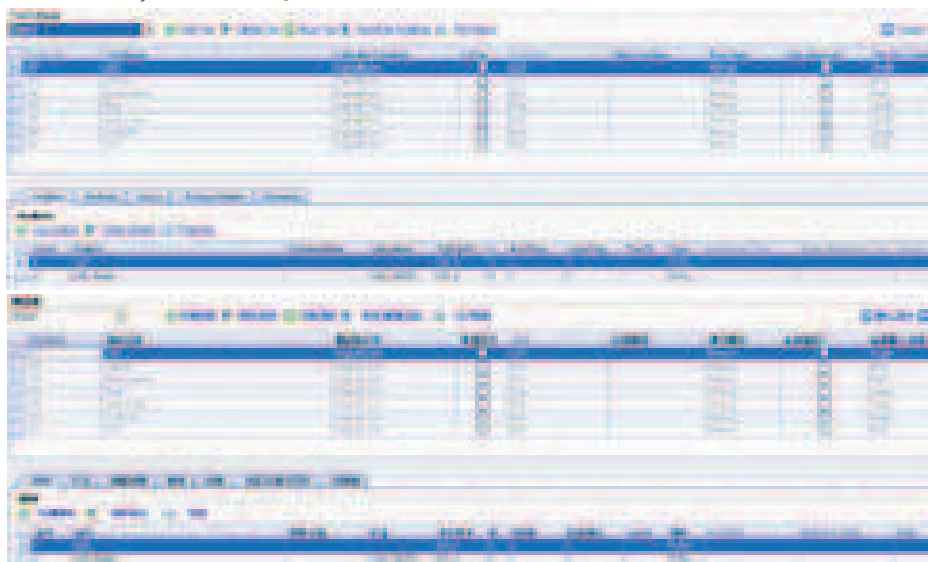
more server machines to the cluster.

Intuitive Graphical User Interface

To reduce the training burden, the clinical trial LIMS must be easy to use. An intuitive user interface starts with a personalized dashboard that provides at a glance access to key performance indicator (KPI) data as well as dynamic task notification of work pending for specific users. The STARLIMS dashboard screen shown below illustrates possible KPIs presented in a variety of formats as well as a console showing outstanding work for the user.



To support ease of use in emerging countries, the LIMS should support multiple languages simultaneously on the same system. For example, the STARLIMS Test Manager screens below show the same information from the same system, but in two different languages; English and Chinese.



Imagine an eDC system that could collect and transmit data anywhere in the world...



...even the Masai Mara.

In Africa only 4.7% of the population have any level of access to the internet, so if your eDC system requires an un-interrupted connection to the worldwide web, your chances of success are as remote as the location.

Cmed's innovative Timaeus system offers full function data acquisition and management not only through the web but using satellite, GSM and GPRS technology, so doesn't rely on local infrastructure; no landline, no internet, no problem.

To find out more about how Timaeus can overcome the challenges of running remote clinical trials, visit www.cmedresearch.com or call Richard Young on +44 (0)1403 755 081.

Cmed Group Ltd. ◀ Holmwood ◀ Broadlands Business Campus
Langhurstwood Road ◀ Horsham ◀ RH12 4QP ◀ United Kingdom
Telephone: +44 (0)1403 755 050
Fax: +44 (0)1403 755 051
E-mail: contact@cmedresearch.com



Driven by technology. Guided by experience.

To streamline data entry and avoid data entry errors, the clinical trial LIMS should support bar code scanning and double blind data entry. To guide proper specimen handling and data collection, the LIMS must also display relevant instructions to support personnel during specimen collection, storage, shipping, and testing activities.

Ability to Implement Business Process Changes

To establish operations in emerging countries, clinical trial operations personnel must be able to initiate new sites quickly. Furthermore, they are faced with a dynamic and competitive environment that can often change without warning. New regulations, new cost structures, and unplanned disruptions to operations all contribute to these challenges. Managing a trial requires local logistics expertise and constant monitoring of each local regulatory environment. However, these challenges present opportunities for an organization that has the flexibility to adapt to these changes quickly. Any clinical trial LIMS must provide this flexibility to implement the type of business process changes illustrated below:

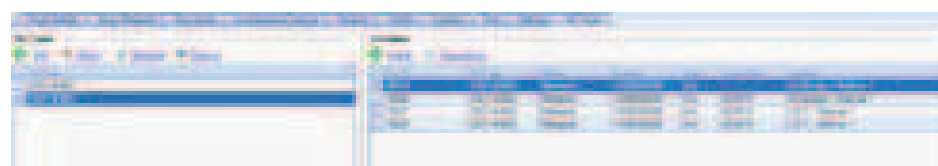
- **Bringing a new facility on line.** A web-based LIMS can be easily deployed to a new facility when increased shipping costs or regulatory restrictions make it desirable to start up a new laboratory or sample handling facility.

- **Integrating new laboratory data.** A clinical trial LIMS that includes an integrated Scientific Data Management System (SDMS) can enable automated data acquisition from new laboratory systems (both internal and external) that might otherwise be considered uneconomic, or too time consuming, to integrate. STARLIMS is seeing its unified SDMS/LIMS being used to enable electronic test result acquisition from external laboratories. STARLIMS clinical trial customers use the SDMS to parse unstructured reports produced by the external laboratories in pdf, MS Word or other format, store the test results into the LIMS database, and then manage all the necessary business logic relating to the results. Because the STARLIMS SDMS includes artificial intelligence capabilities that greatly simplify and streamline the parsing of an external laboratory's report file, it has lowered the barriers to implement these interfaces. Electronic acquisition of this external lab data provides more immediate visibility to all stakeholders in the clinical trial.

- **Managing changing kit requirements.** Local transportation requirements may dictate that kits vary by country or site. The LIMS should allow flexibility to define local variations in labeling and specimen collection or transit container requirements.

- **Using backup laboratories.** A user- configurable clinical trial LIMS should easily allow specimen to be redirected to a back up laboratory in the event of a laboratory or instrument breakdown. The LIMS should also have the flexibility to support differences in laboratory methods and reference ranges used by the various laboratory sites..

- **Changing supply chain management.** With poor logistics infrastructure in emerging countries, supply chains are under frequent stress. By closely tracking inventory levels of kits and other supplies, the LIMS can allow operations personnel to optimize the use of existing inventory, transfer specimen collection supplies, or give direction for suitable handling alternates to avoid the multitude of issues that can arise from samples collected and shipped using the wrong containers and materials.



Subject Management

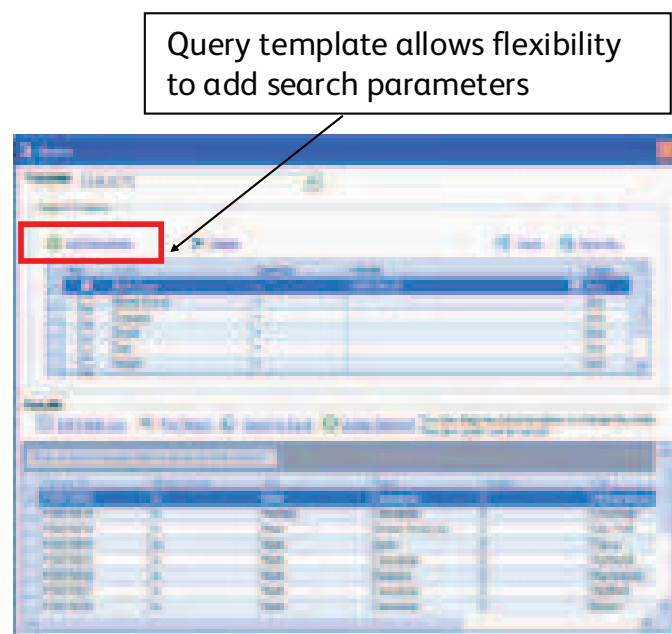
In order to take advantage of the patient pool in the emerging markets, the clinical trial LIMS should include powerful tools that

manage subject recruitment, consent, and all demographic, clinical, and laboratory test data.

- Patient consent information must be managed to a level of detail that ensures all human biological specimens are handled per IRB and regulatory requirements, and in accordance with donor preferences. The LIMS should manage consent detail at both the subject and specimen level. The STARLIMS biorepository module shown below illustrates the capture of consent detail at the specimen container level.



The system should manage demographic and clinical detail for clinical trial subject candidates and provide tools to view historical test results, attached files, and special notes. Powerful and flexible query tools are needed to identify subject candidates for a particular study. For example, the query template illustrated below provides a convenient and user-modifiable search tool that can be used to identify suitable candidates.



Query/Issue Identification and Resolution

The challenging environment in emerging countries can create issues or discrepancies that must be managed and resolved. To give the operations personnel the ability to manage the clinical trial, they need immediate visibility to any potential issue that could impact data quality or compliance to protocol requirements. Time is a very precious commodity in this situation. Any potential query (issue) that may impact the availability or quality of the data generated through the laboratory must be identified, assigned, and investigated promptly. As time goes by, the ability to successfully resolve a

query is reduced exponentially. For example, the sooner a call is placed to the clinical site, the greater the likelihood that the clinical site will be able to locate a missing sample and ship it before the sample stability

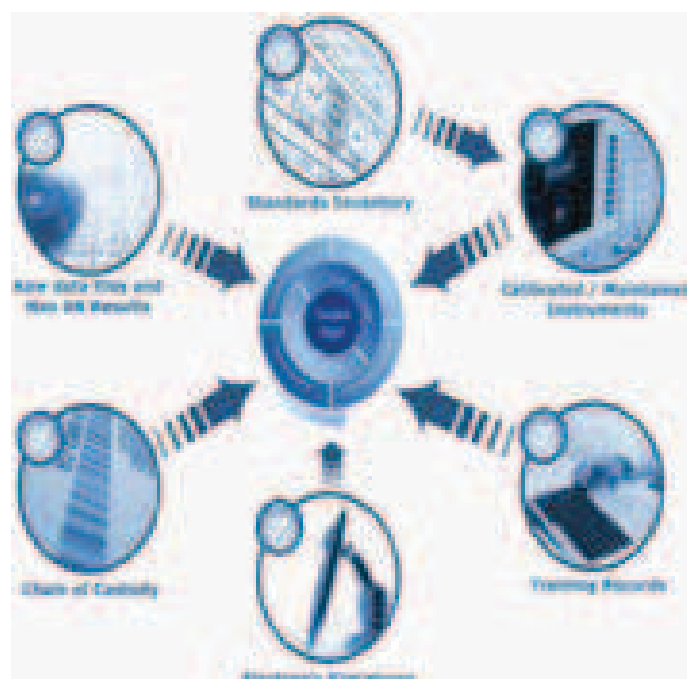
period expires. Efforts to address discrepant or missing data are much more likely to be successful the sooner the follow up effort is initiated following the original collection/recording of the data. As time elapses, the greater the chances that the clinical site personnel involved will not remember important information or will not be available to answer relevant questions. Furthermore, prompt feedback to the clinical sites regarding recurring patterns of issues can be an effective tool to drive continuous improvement and eliminate issues/queries by their root cause.

A LIMS that effectively integrates sample management (accessioning, specimen testing, routing, and storage) with a detailed definition of the clinical study enables early detection and prompt resolution of issues/queries. As a specimen undergoes different steps in a collection, shipping, and laboratory workflow (ship, receipt, test, report, store) the LIMS can find deviations by comparing the actual condition, or result, to the requirements specified in the LIMS clinical study manager. Furthermore, the LIMS should include an issue/query management tool so that items can be tracked, managed, and assigned until each is resolved. A clinical trial LIMS that is well integrated with biorepository/specimen storage management features will also allow personnel to manage the logistics related to shipping and receiving specimens, query the status of specimens that are in transit, and find alternative specimens for a given subject in the event that the original is lost or damaged.

Regulatory Compliance

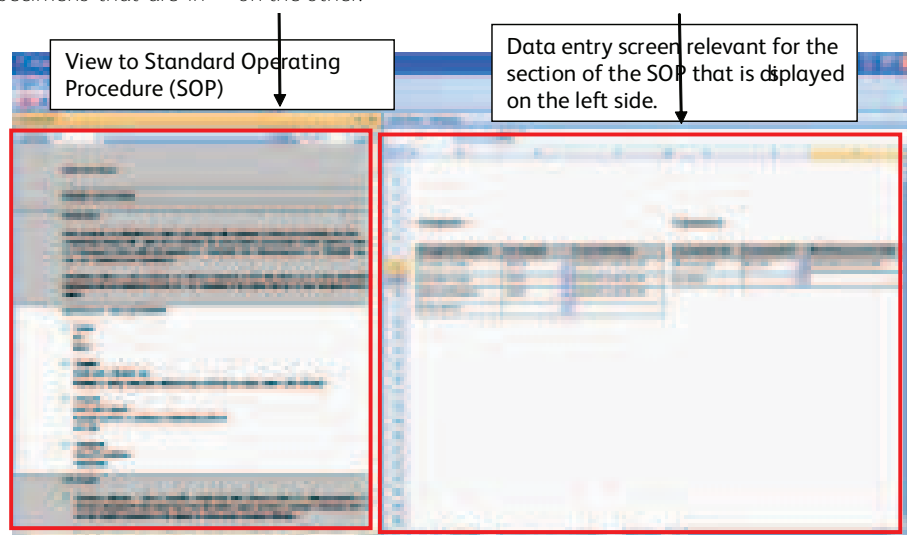
Even though emerging countries can have regulatory variances on GCP and ICH guidelines, the clinical trial LIMS should provide complete support for GCP, ICH, 21 CFR part 11, and GLP compliance for maximum flexibility and utility. To support compliance in this tightly regulated environment, the ultimate goal is to ensure that all the data produced by the clinical trial laboratories is defensible. To this end, the clinical trial LIMS must document and provide easy access to data that demonstrates:

- Proper chain of custody and specimen handling by authorized and trained personnel throughout the sample life cycle.



- All kits, testing reagents and standards used were not expired
- All laboratory analysts were properly trained and certified
- Clinical laboratory analyzers were properly calibrated and within their preventative maintenance schedule.
- 21 CFR part 11 compliant electronic signatures
- Access to data that supports the final test result, such as raw instrument files and all laboratory worksheets, to demonstrate adherence to laboratory standard operating procedures (SOPs)

Integration of an Electronic Laboratory Notebook with the clinical trial LIMS can boost lab productivity and quality as well as improving regulatory compliance. An Electronic Laboratory Notebook is designed to map and enforce processes defined in Standard Operating Procedures to workflows in the system. This ensures that the SOPs are adhered to at all times and provides the process traceability needed in clinical trial laboratory applications. It also records all the relevant data associated with the testing or analysis being undertaken (which may go well beyond just the results obtained). For example, the STARLIMS Electronic Notebook screenshot below shows a split screen where the SOP for a urine culture is displayed on one side while the notebook data entry form for the specific step or section of the SOP is displayed on the other.



Summary

Recruitment of subjects is a bottleneck in most clinical studies. Expanding studies to emerging countries allows clinical trial sponsors to expand the pool of available subjects and investigators. A flexible and powerful clinical trials LIMS can help overcome the additional challenges that are associated with running studies in these areas. Key attributes of a successful clinical trial LIMS must include: web-based access, user-friendly user interface, flexibility to implement business process changes, subject management and query identification and resolution tools, and regulatory compliance. ■



Ed Krasovec is the Director of Clinical Operations for STARLIMS Corporation. He oversees business development, project implementations, and product management for clinical laboratory information management applications, including clinical trials, biospecimen management and healthcare. Ed was the founder of an oncology patient management software company and has been leading the development of cutting edge laboratory and clinical informatics solutions for the past 10 years. He also has over 15 years of management and technical experience with DuPont in laboratory management, business planning, sales, research, and operations. Ed holds a BSc in Chemical Engineering from Penn State University and an MBA from Drexel University. **Email: Ed.Krasovec@starlims.com**

ILSI Biomed Israel 2009

ILSI Biomed Israel 2009

ILSI Biomed 2009 follows the success of previous annual conferences. For the eighth year in a row the Israeli life science community gathered for the ILSI Biomed conference which was held June 15-17 in Tel Aviv. ILSI Biomed is both Israel's premier life sciences conference and a leading international conference covering the fast-growing, innovative field of healthcare and life sciences industries. It showcases Israel's most advanced companies and technologies. The conference attracted 6000 participants from Israel and abroad, mainly industry leaders, scientists, researchers, venture capitalists, and angel investors.

We were delighted to see such a high number of participants as it matched last year's record number of approximately 800 visitors from abroad, representing close to 40 countries with the largest number of attendees coming from the USA, France, Italy, the UK, Germany, the Czech Republic, Denmark, Russia and China.

ILSI Biomed 2009 provided attendees with insights into the underlying drivers of future changes in the biopharma and medical device industries. As the market environment toughens, new business models are evolving. Large pharma attempts to focus and emulate biotech creativity while biotech strives for a more expansive operating mode. The various keynote speakers focused their talks on strategies for thriving in this tough economic and regulatory environment, dealing with the upcoming healthcare reform in the USA and its rippling impact worldwide.

The conference opening session was delivered by the Honorable Mr. Shimon Peres, ninth President of the State of Israel. The talk was a moving and remarkable account of his view of the most revolutionary technology changes to come about over the next decade and Israel's role and contribution to these important developments.

It is worthwhile mentioning several of the keynote speeches given by Allergan's and Covidien's CEOs, who each focused on their strategies for growth; Roche's Head of Pharma's R&D who discussed Roche strategy for its pharma product pipeline; Astellas' Head of Business Development who talked about the globalisation of the Japanese pharmaceutical industry. Avalere Health's President and Founder presented his views regarding the face of change: regulation, legislation and the US markets. Lazard Healthcare Group's Managing Director discussed biotech and medtech – navigating through rough seas.

ILSI Biomed 2009 highlights:

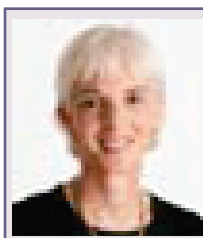
- o Plenary sessions and presentations by industry leaders and academia worldwide
- o The 3rd International Stem Cell Meeting
- o Unique opportunities for networking and learning
- o Satellite events focusing on clinical studies, regulatory issues, country-specific symposiums
- o Over 2500 one-on-one partnering meetings
- o Academic institutions' technology transfer event
- o Exhibition of the latest medical innovations

This basket of events offered a unique opportunity to gain full access to the latest information available in the field. Furthermore, the networking events offered the opportunity to meet a vast variety of Israeli biopharma and medical device entrepreneurs, major pharmaceutical companies, life science research leaders, policy-makers and internationally prominent industry investors, to explore business relationships.

We were proud to host Dr. Jesse Goodman, Chief Scientist and Deputy Commissioner, US Food and Drug Administration, whose keynote lecture focused on strategies to facilitate innovation in medicine and public health. We were also lucky to have three FDA staff members who talked about the evaluation of medical devices at CDRH.

I would like to close this brief description of the conference by giving very high marks to the 62 Israeli medical device, pharma and biotech companies who gave their best to make it a very successful conference. It is their innovation and drive that attracts this great audience who come to listen and interact with the best of what Israel has to offer in the life sciences.

ILSI is a non-profit organisation, representing the mutual goals of approximately 800 Israeli life science companies. Its mission is to research, develop and advocate policies and actions that promote medical device, biotechnology, pharmaceutical and ag-biotech in the State of Israel, and increase awareness of its strength and innovation worldwide.



Ms. Rutí Alon joined Pitango, Israel's largest VC fund in 1997. With over 25 years of international experience in the high-tech medical industry, Rutí is a General Partner investing in life sciences companies. Ms. Alon previously worked on Wall Street where she held senior positions with Montgomery Securities and Kidder Peabody & Co. Ms. Alon is the Chairperson of ILSI since its inception in 2005. **Email:** ruti.a@pitango.com



Q-Trials

Israel's Gateway to Clinical Trials

Industry-leading Clinical Trials delivery via a skilled, highly trained and dedicated team of locally-based CRAs

Q-Trials - Israel's Global CRO offers support for your local and international studies:

- > Competitively Priced
- > ICH-GCP & Local Regulation Standards
- > Phase I through IV Studies
- > Feasibility & Site Selection
- > EC & CA Regulatory Submissions
- > Monitoring & Management
- > ICF Translation & Adaptation
- > Document Development
- > Pharmacovigilance
- > IMP Labeling, Importing & Dispatching
- > Clinical QA Audits
- > Co-source at Client Location



To learn more about what Q-Trials can offer you
please see our website at www.q-trials.com

Tel: + 972-8-9714919 Fax: + 972-8-9718184 Modiin, Israel

Bringing outsourcing to CPhI

ICSE - the International Contract Services Exhibition

ICSE is the international stage, within CPhI, for companies providing outsourcing services in Clinical trials, Contract research, Custom manufacturing, Biotechnology, IT, Analytical services, Packaging services and Logistics. ICSE represents every sector and major disciplines of the pharmaceutical industry, making it the must-attend event for any business or individual in the contract services and clinical outsourcing sector.

Go to www.icsexpo.com to register for ICSE 2009 or e-mail icse@ubm.com

13-15 October 2009 **icse**
Feria de Madrid, Spain bringing outsourcing to CPhI

THE INTERNATIONAL CONTRACT SERVICES EXHIBITION



Specialist in pharmacokinetics and proof of concept in target population which serve as pharmacological models. Phase I & IIa in patients is the core business in private hospital settings. www.ipr-ee.com



ABL's clinical trials services maintain the vital link between study sites and the laboratory putting it through multi site sample coordination.



PDP is a Global Premium courier dedicated to the Clinical Trials and Life Science Industry. When you need to ship your time and temperature sensitive diagnostics specimens, Investigational materials, medical supplies and dangerous goods. Trust PDP. www.pdpcouriers.com



A leading global CRO, Kendle International delivers innovative clinical development solutions to maximise product life cycles and grow customer market share. www.kendle.com



Medidata Solutions (www.mdsol.com) is committed to providing life science organisations the most advanced tools for planning and managing clinical trials.



Through its impeccable performance as CRO, Congenix tries to contribute to global process offering a full range of services in the CIS and CEE. www.congenix.com



The Temmler Group with 7 European production sites offers innovative solutions, efficient manufacturing and highest flexibility for your Pharmaceutical Products. Email: ctm@temmler.eu



For more than 60 years, Charles River has provided tailored research models and laboratory animal support services, as well as preclinical and clinical services, to help our global partners accelerate their research and drug development efforts. Our offerings span the entire drug development process, from discovery through market approval, forming a seamless partnership throughout the process. www.criver.com



Midsize CRO, broad range of personalised services, international capabilities, regulatory, nonclinical, CMC, clinical, client satisfaction, quality service, people, data, proven track record. www.cato.com OR email: info@cato.com



Synergy Research Group is a Russian CRO, successfully operating in Russia since 2002. SynRGTM offers services for conducting clinical trials- from study approval to pharmaco-economic survey. Represented in Moscow, Saint-Petersburg, Novosibirsk, Yekaterinburg, Perm and Almaty (Kazakhstan). istefanov@synrg-pharm.com



Dr. Oestreich + Partners GmbH was founded in 1991 as full-service CRO, with its headquarters in Cologne, Germany, one of the most densely populated regions of western Europe. We are engaged in implementing: running and statistically evaluating clinical trials phase II to IV and PASS projects over the last 18 years. www.OandP-CRO.com or OPinfo@OandP-CRO.com



Thomson Reuters is the leading source of intelligent information for professionals around the world. Our customers are knowledge workers in key sectors of the global economy. www.thomsonreuters.com



Medical translations for clinical research, registration, pharmacovigilance and use of medicines. All European and many non-european languages. www.medilingua.com



Is specialised in tailor made insulated packaging solutions, made of injected polyurethane foam, which gives excellent insulating performance, especially when combined with our one-piece production method www.Exampackaging.be



Capturing data anywhere in the world, anytime of the day. Only Cmed and only Timaeus can deliver this for you. www.cmedresearch.com



With 25 offices among the world's most populated cities, Pharm-Olam International provides cost effective coverage in both emerging and traditional markets for Phase I to IV studies. Contact Pharm-Olam for a complimentary feasibility study for your next clinical trial. USA: +1 (713) 559-7900 • UK +44 (0) 1344 891121 • info@pharm-olam.com • www.pharm-olam.com



"Q-Trials is a Contract Research Organization offering Professional, Efficient and Reliable support for Clinical Trials. Experienced in a variety of therapeutic areas within the Drug, Device and Biologics Bio-medical Industry, Q-Trials perform Regulatory submissions, Monitoring, Study management and more."



Chubb is a leading insurer of speciality pharmaceutical companies with a global network to efficiently deal with the challenges of local clinical trials insurance certificates requirements. Email: christait@chubb.com



Laminar Medica specialises in the design, test, manufacture and qualification of insulated shipping systems to protect vaccines, drugs and associated medical products from extremes of temperature during transportation. Web: <http://www.laminarmedica.com>, Email: enquiries@laminarmedica.co.uk



eurofins

Medinet

23	Analytical Biochemical Laboratory BV
IBC	CATO Research
44	CenterWatch
59	CMED Group Ltd
29	Congenix LLC
17	Charles River
25	CHUBB Insurance
IFC	CROMOS Pharma
3	Dr. Oestreich +Partners GmbH
27	Eurofins Medinet
31	EXAM Packaging SPRL/BVBA
35	Global Engage Ltd. – The China Clinical Trials Outsourcing Congress
62	ICSE – International Contract Services Expo
50	IIR – Partnerships in Clinical Trials 2009
7	INNOPHAR GmbH
53	INTERLAB Central Lab Service – Worldwide
5	Laminar Medica
11	Kendle
15	Medilingua BV
9	Medidata Solutions Worldwide
37	MESM Ltd
33	Oxford Global – 2nd annual Proteins Congress
19	PDP Couriers
39	Pharm – Olam International
13	QCTN – Queensland Clinical Trials Network
61	Q-Trials Ltd
47	Synergy Research Group
21	Temmler Pharma
OBC	Thomson Reuters
42	Vienna School of Clinical Research

JOURNAL FOR
CLINICAL STUDIES
Your Resource for Multisite Studies & Emerging Markets

Subscribe today at
www.jforcs.com
or email at
info@pharmapubs.com



Ever wondered, why we choose these flowers as the Front Cover of JCS? **Each flower represents the National Flower for the Emerging Countries.** I hope this journal guides you progressively, through the maze of activities taking place in these Emerging Countries.

Journal for Clinical Studies - Your Resource for Multisite Studies & Emerging Markets (JCS) is also available from Center Watch Today.
Please visit: www.clinicaltrialstoday.com

In Concert with Quality Research

Cato Research offers the ideal balance
between international capabilities
and personalized CRO services.
We will orchestrate your success.

Integrated Drug Development

Regulatory Affairs

Non-Clinical Safety

CMC Consulting

Clinical Trials

Pharmacovigilance

Data Management and Statistics

Audits & Compliance

CATC
RESEARCH

Quality People Quality Data Quality Service

Boston | Bucharest | Cologne | Canton | Frankfurt | Gsta | Heidelberg | Johannesburg | London | Madrid | Rio | San Diego | San Francisco | Seoul | Washington | Zagreb
Cato Research Ltd • 4344 South Alston Avenue • Durham, NC 27713 • USA • Phone: (+1) 919.341.2084 • Fax: (+1) 919.341.2097 • VoiceMail: (+1) 919.341.099
Email: info@catc.com • Website: www.catc.com



IMAGE COPYRIGHT: THOMSON REUTERS

REGULATORY SOLUTIONS FROM THOMSON REUTERS

KNOWLEDGE AND EXPERT SERVICES TO ENSURE YOU INTERACT
WITH AUTHORITIES SWIFTLY, ACCURATELY AND SUCCESSFULLY

From global regulatory intelligence to product lifecycle consulting, we'll help you to stay fully up to date with your regulatory requirements, streamline your processes, better position your organization and your products, and keep your projects on-track despite all the other pressures on your department.

KEY SOLUTIONS

IDRAC®

A single source of trusted global regulatory intelligence.

With *IDRAC* supporting your regulatory decisions, you can gain competitive advantage and minimize risk.

IDRAC equips your organization to stay fully up to date with the regulatory requirements in your target markets.

Only *IDRAC* has the global reach, depth of analysis and local expert knowledge to keep you informed of every regulation that could affect your product.

This is why *IDRAC* is the solution the world's most demanding pharmaceutical companies rely on to support their regulatory decisions, day after day.

Liquent InSight®

A centralized, global view of regulatory documents and submissions.

Thomson Pharma®

Comprehensive global pharmaceutical information solution.

Prous Science Integrity®

Integrated drug discovery and development portal.

Contact us for further product information at
go.thomsonreuters.com/rss



THOMSON REUTERS