May 2010

JOURNAL FOR CLINICAL STUDIES

Your Resource for Multisite Studies & Emerging Markets

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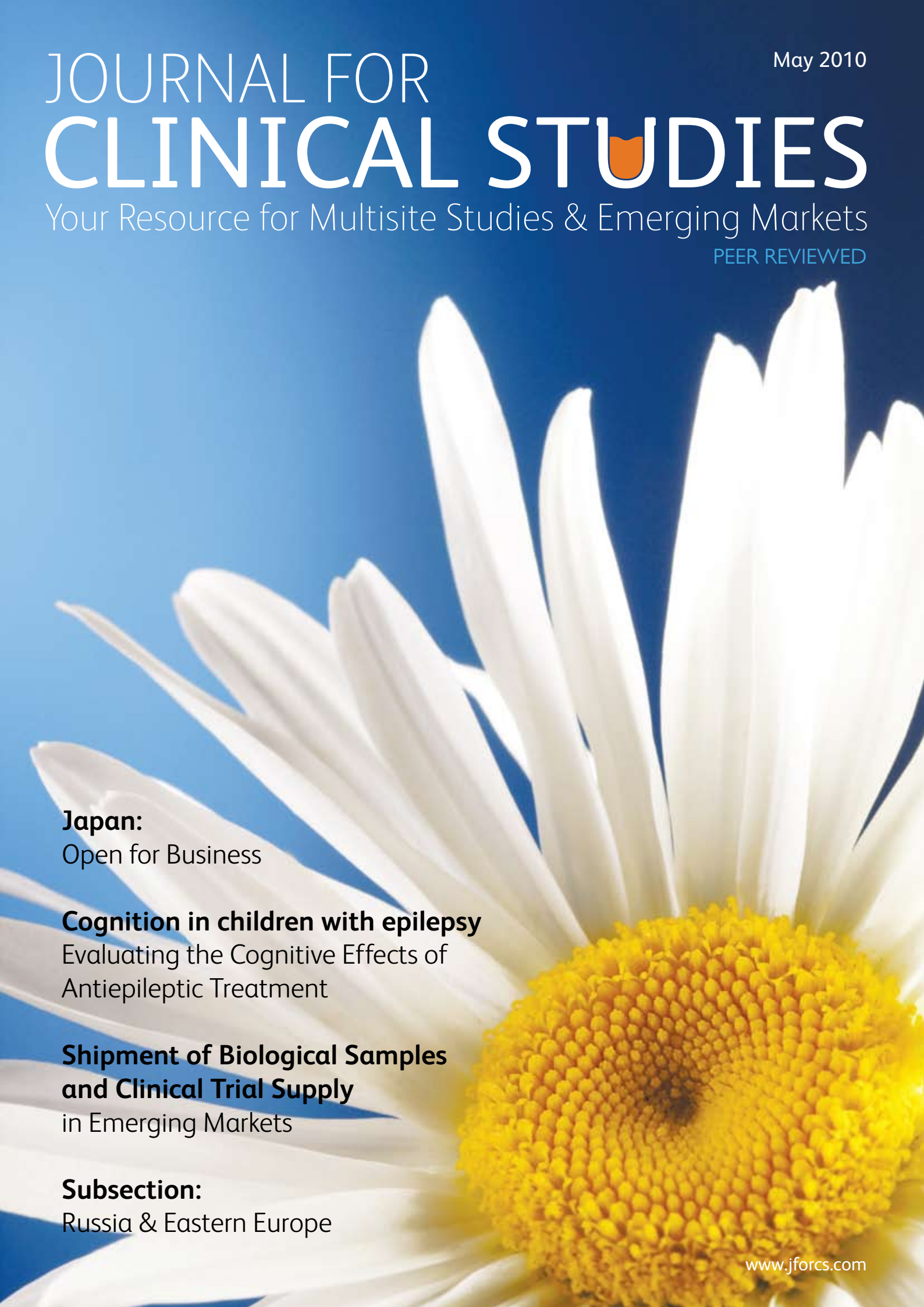

Japan:
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PUBLISHED BY:
Pharma Publications
www.jforcs.com
Address: Building K Unit 104
Tower Bridge Business Complex
Tower Point
London
SE16 4DG
Tel: 0044(0)2072375685, Fax: 0044(0)2073947415
Email all correspondence to: info@pharmapubs.com

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

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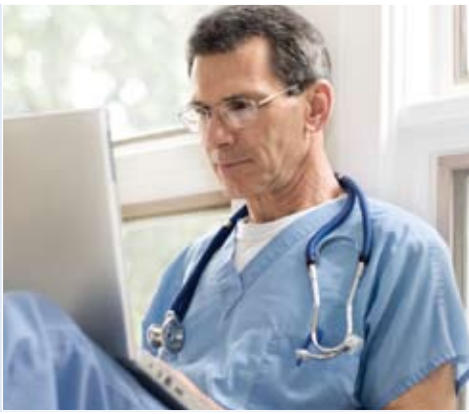

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Editorial Advisor Keynote

It is evident that those who have their heart and soul in clinical trials had been writing in the JCS since its inception; as a matter of fact JCS never ceases to amaze me with the amount of in-depth and detailed information about doing clinical trials in faraway places. In this issue ***Donald F. Grabarz of International Regulatory Consultants LLC*** contemplates the conduct of clinical studies in sites other than the United States or EU member states, while ***Russell Neal of Clinical Research Network (CNS Pty. Ltd)*** describes the return of optimism in the industry and easing of money flow with developers planning ahead.

One can never undermine the value of local knowledge. The situation in Latin America with regards to the resourcing solutions model is a challenging one, as explained by ***Oscar Podestá of Chiltern International***, while ***Malgorzata Szerszeniewska, the MD and CEO of EastHORN Clinical Services*** explores the high level of variation in the cost of conducting clinical trials in Central and Eastern Europe, Latin America and Asia. But can Russia, Ukraine and Eastern Europe help biopharmaceutical companies to bring the product to market in a cost-effective way? This question is analysed by ***David Passov of ClinStar***. On the same lines ***Rani Abraham of ClinTec International FZ-LLC*** explains the under-discovered potential of running clinical trials in the Middle East and North Africa. As she put it; "this emerging market now holds a high potential for clinical trials"; and ***Dr. Guy Patrick of Centrical Global Limited*** discusses ways of tapping into the appealing prospect of conducting clinical trials in emerging markets in a calculated way.

Chris Tait of the Chubb Group of Insurance Companies talks about the growing concern that Europe is seen as a complex and expensive place to run trials and therefore is possibly losing out on trial activity; but would a simple process help to reduce costs by reducing expensive overages of study medication? Just-In-Time packaging and labelling is explained by ***Dr. Claudio Alexander Lorck of Temmler Werke GmBH***.

Japan, a key ICH member, has often been regarded as one of the more challenging venues in which to conduct clinical trials and obtain licensing for new medicines. However, it is now declared "open for business" as explained by ***Alberto Grignolo, PhD & Yoshitaka Aida, DVM, PhD*** in the regulatory watch page.

The Cardiovascular Safety Watch section provides interesting information about automated reading of electrocardiogram (ECG) intervals by ***Dr. Rick Turner of Quintiles Cardiac Safety Services***, while ***Alison Bond & Katherine Hutchinson of Quanticate*** explore why pharmacovigilance has a vital part to play in the avoidance of adverse effects of medicines.

In the therapeutic section, ***Anna La Noce of Pharmanet Development Corporation*** explains why an increase in the number of clinical trials dedicated to the evaluation of cognitive effects of antiepileptic treatment in children is expected in the future. It is also worth reading about naturally occurring substances that can enhance cognitive function; the rationale for such self-medication is discussed by ***Dr. Keith Wesnes of United Biosource Corporation***.

We hope that you enjoy reading this issue, and we look forward to seeing you all at the DIA Annual Meeting in Washington. ●

Dr. Maha Al-Farhan, M.Phil, M.B.A, CCRA, President and CEO, ClinArt International.

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US FDA and EU Foreign Clinical Studies Dilemma

Contemplating and conducting clinical studies in sites other than the United States or EU Member States can more often jeopardise the utility of the data obtained in seeking regulatory approvals. In today's economic environment when small companies recognise the need to conduct a clinical study they will often attempt to minimise the cost of a study. The strategy such companies use is to conduct their study in countries where the cost appears to be attractive when compared to that of the US or EU. In addition to the cost issue, other attractions are often prompted by the appearance of less regulation and the perception of more timely results. The reality is that more often than not the outcome sought is not realised.

Policies and perceptions of regulatory authorities such as the FDA, and similarly EU Authorities, will not accept foreign clinical studies as the sole basis of review for safety and/or effectiveness. While there are perhaps a multitude of reasons for agencies such as the FDA not accepting foreign studies, the most prevalent relates to a long-standing policy held by the FDA in requiring clinical studies to have been conducted in the US. Call it mistrust or distrust, the reality prevails. Experience has shown that attempts to convince the regulators in the US are more than an uphill battle. The complexities of trying to convince the FDA to accept foreign clinical studies is far more complex than one realises. While many companies have a simplistic view of the FDA being a singular entity, the truth is that the FDA is a multi-discipline complex government organisation comprising many review groups and reviewers responsible for clinical study submissions and data review. Based on their collective and individual experiences the interpretation and application of the policies associated with clinical studies will vary.

Companies should not abandon their plans to conduct clinical studies outside the borders of the US or EU. In so choosing, the company planning needs to clearly understand the issues and to address both the need and desire to conduct clinical studies in countries outside the US or EU. As simple and as contrary as this may sound in consideration of the issues discussed above, it is not without reason. There are numerous factors and approaches given the nature of a contemplated clinical study. It is not a one-size-fits-all situation.

Perhaps the most prevalent and influential consideration is that of ethnicity. A study for certain compounds which target a clinical condition found in a particular ethnic population is one example where the general policy rules of the regulators may not apply. In such cases a company would be well advised to approach the FDA or appropriate health authority within the EU before commencing a study. This will help to both educate the regulatory authorities and to help ensure the usability of the data obtained towards product approval.

As a general rule, and when in doubt, a meeting with the regulatory authorities is more than highly recommended. As referred to in the US, this would be an Investigation New Drug (IND) or Investigational Device Exemption (IDE) pre-submission meeting. This affords the opportunity to present your plan and to also educate the regulatory authority who would otherwise be responsible for the review and approval of both your clinical study and ultimately your product. The advantage to such a meeting will provide guidance for the company in not only the study details, but also as to the ultimate acceptability of the study as well as the product. The consideration of the expense and cost for a pre-submission meeting pales when compared to the unexpected cost of a rejection, not to speak of the time lost.

In consideration, when one looks at the contemplated effort companies exert in both time and expense to develop a marketing strategy for their products, in comparison, the time and expense to explore and develop a realistic strategy to pursue a clinical study is small. While the costs associated with a clinical study are significant, the notion that short-cuts can be achieved, saving money and reducing timelines, is a myth. ●

Donald F. Grabarz is a co-founder and Managing Director International Regulatory Consultants, L.C., serving the medical device, in-vitro diagnostic, pharmaceutical and biotech industry on regulatory, clinical and quality matters. Mr. Grabarz is a Pharmacist by profession having received his degree from St. John's University in New York City. He has also studied at Pace University and attended courses provided by the Wharton School of Business. Prior to IRC, Mr. Grabarz has had over twenty plus years of industry experience with significant management responsibilities in major corporations such as Johnson & Johnson, Becton Dickinson, CR Bard and Symbion. He was actively involved in the evolution of the Medical Device Amendments of the US Federal Food, Drug, and Cosmetic Act as well as in the development of Safe Medical Devices Act, and those implementing regulations. Mr. Grabarz has lectured extensively throughout the U.S., Europe and Asia on a variety of regulatory subjects. He has also authored feature and topical articles to various domestic and international professional trade publications. His experience also has included work on DEA, EPA, HCFA and OSHA matters.

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Australasia Watch – May 2010

I have been fortunate to have attended a number of trade shows around the US and Europe recently, such as BioEurope Spring and BIO in Chicago. I continue to find these events very useful in gauging the mood within our industry. Investment is of course the lifeblood of the biopharma industry, and the last few years have been a tough period for many, not just those seeking investment for the development of their IP but also those who support the research and development of that IP such as CMOs, CROs, etc.

I have been encouraged to see a clear return of optimism to our industry, driven quite clearly by the improvement of money flow, with a number of companies releasing press statements on their funding success. BIO in particular was very vibrant, and it was clear to many who attended that not only was the intensity of the partnering meetings better this year, but there continues to be a view that many developers are planning further ahead, something that perhaps was not seen at the height of activities during 2006/07. This may be a reflection of a raising of the investment bar, and with it more onus resting on sponsors and developers to consider longer term financial needs, past initial non-clinical needs but through to mid-stage clinical trials.

What then does this renewed positivity mean to Australasia?

Well, quite a bit, it seems, with three very exciting developments announced recently.

Firstly, DSM Biologics announced at BIO that they have signed a preliminary agreement to enter a partnership with the Queensland State Government as well as the Commonwealth of Australia to design, build and operate the first major Australia-based mammalian biopharmaceutical manufacturing facility, which will be located in Brisbane. This finally fills a vital gap in the long list of local services that will appeal not just to Australian developers but to international sponsors as well.

Furthermore, Cappello Capital Corp launched its Australian Desk at the end of May. Cappello is one of the largest and most experienced Australian-focused investment banking desks on the US West Coast, and with heavy-hitting Australians leading this initiative, such as Paul Hopper and the former Australian Minister for Foreign Affairs, the Hon. Alexander Downer, this is another indication of the attractiveness of Australia, in terms of both its intrinsic product discovery opportunities as well as its history as a quality region to perform core clinical studies in support of such investment.

As if that wasn't exciting enough, Queensland and Indianapolis-based Eli Lilly and Co have created a $250 million venture capital fund to expand and develop the biotechnology industry. Announced by Queensland Premier Anna Bligh in a recent statement, Lilly has pledged up to 20 percent of the fund, while the Queensland government has contributed $25 million. Other unnamed strategic US investors have also agreed to participate with the as yet unnamed venture fund, to be based in Brisbane, which will focus on biotechnology investments in Australia and southeastern Asia.

An exciting few months indeed for Australia, and Queensland in particular, and putting the increased vibrancy observed at BIO Europe Spring and BIO together with the ethics/regulatory streamlining activities discussed in my last Australasia Watch, the future for product development and clinical research in Australia continues to look bright. ●

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

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Challenges for the Resourcing Solutions Model in Latin America

As Chiltern's General Manager in Latin America, one of my primary responsibilities is to ensure high quality delivery of our services in the region. Upon joining the company several years ago when Chiltern first entered the Latin American market, I was immediately impressed with our Resourcing Solutions business dedicated to complementing our traditional Clinical Research Organisation (CRO) business through innovative contract staffing. Resourcing Solutions had already established a strong market and reputation with pharma and biotech companies elsewhere in the world, and the Latin American market was already comfortable working under a contract staffing model well before the introduction of international CROs in the region over a decade ago. Prior to Chiltern, my exposure to staffing models was only local and regional, and thus working with a global group provided a greater awareness of both the challenges and opportunities faced when considering contract staffing.

In line with the rest of the world, demand for staffing services in Latin America has increased over the years. Though standalone staffing companies exist, several traditional CROs have added staffing services to their portfolio in which the CRO is responsible for providing the client with the human resources needed to carry out their projects internally. There are flexible solutions to meet individual client needs, from fully outsourced projects to fully insourced individuals. Historically, we have engaged these contracts with local affiliates of the pharmaceutical companies, though in the last few years this has become a frequent request from sponsors without a local presence.

The exponential growth of the Latin American clinical research market is pushing for additional resources and the model has proved to be successful, but are the challenges we face (retention, delivery, quality, availability, costs etc.) comparable with other markets such as the US or Europe? I believe they are similar, though the approach to solve them is slightly different.

Major challenges for the insourcing model in Latin America include:

- Focus on minimising co-employment risks (stringent local labour laws and regulations)
- Clear identification of roles and responsibilities of the Clinical Research Associate (CRA) Acceptance of the CRA as a team member
- Alignment with client objectives and corporate culture
- Close interaction at senior management level (sponsor/CRO) - we need to know what is going on to better support the team and the studies
- One size does not fit all - every country requires a different approach

These have a strong impact on retention, flexibility and cost. In our experience, the sense of belonging has a positive influence on our low turnover. Chiltern invests time, energy and money to provide our Resourcing Solutions staff with the same benefits, career opportunities, training, education and support as employees in other departments of the company. Integration and team interaction is a key factor with a strong cultural background. At Chiltern in Latin America, there is no differentiation between external and internal staff; our staff is the same. This model provides us with the flexibility to have highly trained staff available and to allocate the best resources to each project.

Local and regional affiliates have a clear preference for insourcing/resourcing solutions over contract staffing or temporary staff, which is fairly standard when it comes to global contracts. The main reasons are that this minimises co-employment risks, provides quick availability of well-trained resources and has a low staff turnover.

It is critical to add value at all levels. We have found creative ways to add value despite not being in control of the project. To drive client attention to this service, fair and competitive pricing is necessary. For CROs providing contract staffing options, this requires solid local/regional business units that maintain low overhead costs.

Requests and expectations from local affiliates in Latin America are slightly different from those for global contracts. A successful model in the region takes more than just staffing; it requires a deep knowledge of the local environment and willingness to adapt the cost structure to a very competitive market.

CROs maintain a good relationship with their client by providing a wide range of candidates with the skills and experience required to deliver a successful clinical study. Both staff and clients benefit from working via a CRO environment with appropriate management, support and training. ●

Oscar Podestá is General Manager for Latin America at Chiltern International. He holds a university degree in Biochemistry with more than sixteen years experience in research, a Fellowship in Clinical Microbiology and further specialization in Virology. Mr. Podestá developed a career in the microbiology and infections control field, working on epidemiology programs and coordinating clinical studies for new antibiotics. He started in the clinical research industry as Project Manager for influenza surveillance programs in collaboration with the influenza branch at the Center for Disease Control. During the past 8 years, Mr. Podestá has worked in central laboratory services and has held positions in Strategic and Business Development at International CROs and SMOs in Latin America. He is a founding member of the Argentinean Chamber of CROs (CAOIC) and member of the Scientific Committee for the DIA 2010 Event in Latin America. Mr. Podestá is currently responsible for fundraising and marketing for FECICLA, a non-profit organization focused on Ethics and Quality in Clinical Research in Latin America.

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Cardiovascular Safety Watch

In this new regular column, Dr. J. Rick Turner will be highlighting 'hot topics' in drug cardiac and cardiovascular safety. Dr. Turner is Senior Scientific Director, Cardiac Safety Services, Quintiles, and an Affiliate Clinical Associate Professor, University of Florida College of Pharmacy. He is actively engaged in scientific research to advance the 'Science of Safety.' This inaugural column discusses the topic of automated reading of electrocardiogram (ECG) intervals.

A central component of drug cardiac safety assessments is the evaluation of a drug's propensity to prolong the QT interval as seen on the surface ECG [1]. This interval, defined as the length in the time domain from the onset of the Q-wave to the offset of the T-wave, is a representation of depolarisation and repolarisation of cardiac muscle cells. QT interval prolongation is indicative of delayed repolarisation, a phenomenon associated with a serious and potentially fatal cardiac arrhythmia. In rigorously controlled Thorough QT/QTc (TQT) trials, QT interval duration following administration of a placebo is compared with its duration following drug administration, and the degree of drug-induced prolongation assessed.

The 'gold standard' for interval duration assessment has been measurement by cardiologists or cardiac electrophysiologists, a process referred to as fully manual methodology. In recent years, semi-automated methodology has also become widely used. A computer algorithm identifies the relevant ECG landmarks (onset of the Q-wave and offset of the T-wave) in each heartbeat, and calculates the QT interval durations accordingly. Then, a human reader 'over-reads' the computer's placement of the landmarks, either agreeing with (i.e. accepting) them or disagreeing with them. In the latter case, the reader adjusts the landmark(s) using his or her expert judgment, which in turn leads to the automated recalculation of the QT interval duration based on the adjusted landmarks.

There is now considerable interest in going a step further by accepting an algorithm's landmark placements, and hence QT interval duration measurements, without human over-read. Two major purported advantages are greater reproducibility of measurement and quicker processing of a given data set. There is no doubt concerning the time saving. Therefore, the benefit or otherwise of fully automated reading rests with the veracity of statements that interval measurement variability is indeed reduced, and that measurements are accurate. Operationally, accuracy is evaluated by comparing an algorithm's measurements with those of human expert ECG readers.

Different algorithms, and indeed different versions of the same algorithm, vary in how well they meet these standards. While some algorithms reduce variability, this is not the case for all of them, with some paradoxically increasing variability. Likewise, although some algorithms perform accurately on good quality ECG recordings with normal or well defined T-waves, they often falter on ECGs with noise and/or artifacts, and in the presence of T-wave abnormalities. Also, several algorithms read notably longer than humans. Having said this, given that interval duration change scores (the difference between placebo treatment and drug treatment) are of central interest in ICH E14, a certain degree of disagreement with human assessment is not necessarily problematic if the direction of disagreement is consistent. However, this does have implications for absolute interval values, which, in addition to change scores, are also of interest to regulatory agencies.

At this time, it is fair to summarise that automated reading of ECG intervals by carefully selected and validated algorithms in appropriate settings with limited human oversight may serve the Science of Cardiac Safety. These appropriate settings include TQT and early phase studies in healthy subjects with relatively normal and good quality ECG tracings. Given the differences between algorithms, the same algorithm would need to be used for all ECGs from a given study. It will be of considerable interest to follow the evolution of this field in the next several years. ●

Reference:

1.ICH Guideline E14, 2005. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs.

Dr Rick Turner, is Senior Director, Cardiovascular Safety, Quintiles, and Affiliate Clinical Associate Professor, University of Florida College of Pharmacy. He specializes in the design and analysis of clinical trials, with a special interest in the cardiac and cardiovascular safety of non-cardiac drugs. He has published over 50 peer-reviewed papers and 10 books.

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Are Insurance Problems Slowing your Trials Down? Some Insurers are Trying to Rectify this.

It was all very laudable: the European Clinical Trials Directive 2001 was introduced to establish standardisation of research activity in clinical trials throughout the European Community with the aim of ensuring that the rights, safety and wellbeing of clinical trial subjects were protected. Sponsors would find Europe an uncomplicated place in which to conduct trials, and research subjects would be assured that their safety was being managed. In practice things have not been so straightforward.

In an ideal Europe, when the Directive was passed into local laws in 2004, the regulations regarding safety, monitoring, reporting and insurance would be consistent across the various countries. However there is now growing concern that Europe is seen as a complex and expensive place to run trials and therefore is possibly losing out on trial activity because of this. Of course there are many benefits of the Directive (e.g. the EudraCT pan-European database) but the insurance regulations are just one of the areas in which there is complexity. It all stemmed from the vague requirements made in the Directive where it stated that "provision (must have) been made for insurance or indemnity to cover the liability of the investigator and sponsor". The transposition of this insurance provision in the national laws has led to a significant disparity around Europe.

Challenges to the Insurance Market

The principle of insurance regulation for trials is accepted worldwide, but the large, affluent, medicinal product-using population in so many adjacent countries make Europe's insurance disparity more of a challenge. The impact of this complexity means that purchasers of (the mandatory required) cover need to ensure that their insurer has the knowledge and infrastructure to deal with the various requirements. This has created a specialist market because, to respond to this, insurers have needed to know the business. These are three of their challenges and an update on how they are responding:

Policy Cover

Whilst basically the same cover is granted across Europe, each country has its own way of achieving it. For example Germany deals with injuries from a clinical trial as a kind of personal accident insurance, while other countries require some form of legal responsibility to be established and the UK has its own so-called "no fault" coverage tradition. Local ethics committees, now with a greater responsibility but in many cases no expertise in this specific area, need to see the cover evidenced in the appropriate way. In many cases the policy has to be with an insurance company registered in their country. To provide customers with the cover they need across Europe (and elsewhere) it has meant that insurers have needed to make the effort to understand local cover requirements, create legally acceptable wordings and a system to tie them together for one trial. Not all insurers have both the geographical network and the ability to ensure that local covers are issued correctly.

Policy Limits

Each country wants to ensure that there is insurance money available for their population arising from any adverse impact of a trial, so many "ring-fence" the limits required in their country. Thus a sponsor cannot buy even a large, aggregate overall limit for one trial, but must purchase a number of small separate limits for each country. These quickly stack up: for example typically the limit per local trial is at least €5m in Germany, €6m in France, CHF 10m in Switzerland and €4.5m in Netherlands. Other countries such as Italy (which has recently set quite high limits) vary the limit by number of research subjects. Interestingly the UK does not set specific limit requirements at this time. The challenge for insurers is that they are dealing with one identical protocol so if there is a potential claim in one country there will likely be a similar reaction elsewhere. The potential claim could be significant. Responsible insurers need to cap their maximum exposure to ensure they do not face a claim so large it could destabilise the market, as some multinational trials demand limits in excess of €80m. Insurers are willing to work in cooperation with each other and effectively spread the risk to achieve this capacity and ensure that the insurance market is secure for future trails.

Policy Logistics

Readers at the sharp end of finalising a trial will know that there are many twists and turns as the date for the ethics committee's review gets closer. Patient numbers change, investigators get added and removed, and because the insurance certificate that the committee will review has to be accurate it needs to be changed appropriately; often with too little time to do this manually. This places a strain on insurers and insureds alike. This "crunch-time" will always be part of the trials process, but at least one insurer has created an extranet system that will enable sponsors, their CROs or insurance brokers to purchase local clinical trials cover, or make amendments to previously issued certificates online, so that they can be printed out instantly and taken to the ethics committee within minutes.

It is Not Just Insurers who See the Problem

The challenges that face the insurance market are recognised, and there are the beginnings of a move to reconsider the provisions of the 2001 Directive. For example, the European Organisation for Research and Treatment of Cancer is holding an international workshop to address the "Needs for Harmonisation of Clinical Trial insurance in Europe" because it is concerned that the insurance challenges we face in Europe are having the effect of slowing down cancer research. Insurers are doing what they can to expedite the very real issues faced in the clinical trials insurance market, but some changes in the law will facilitate the achievement of the laudable aims that the legislators strived for in 2001. ●

Chris Tait, is the European Life Science Underwriting Manager for Chubb Insurance Company of Europe SE. Over the last 30 years Chris has gained a broad knowledge of the insurance industry. He started his career as a broker before moving into underwriting and held a number of positions within the insurance and reinsurance markets prior to joining Chubb in 1992. Chris has been instrumental in developing Chubb's expertise in the Life Science sector. He is a Chartered Insurer and Fellow of the Chartered Insurance Institute.

Email: christait@chubb.com

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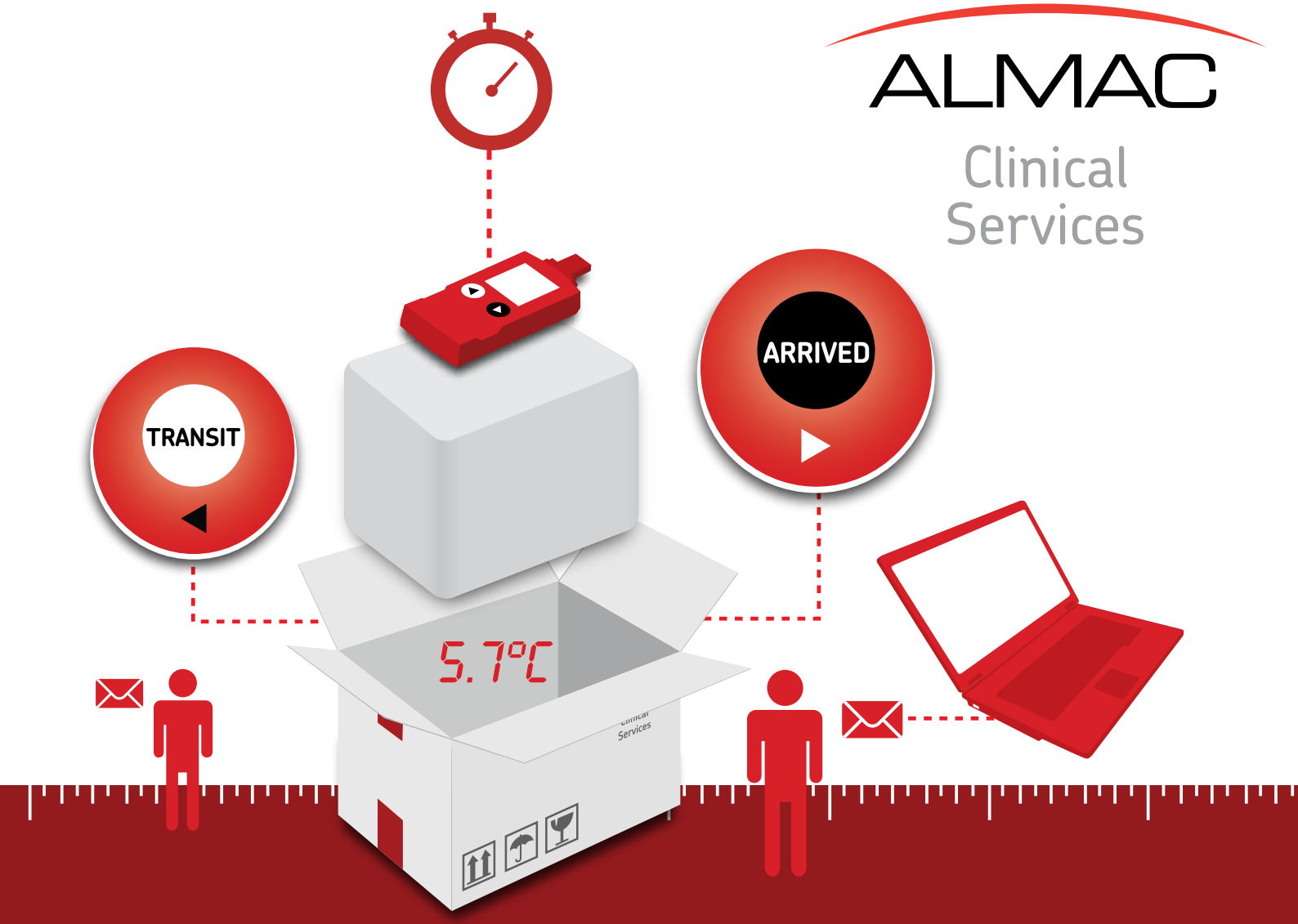

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Benefits of Just-In-Time (JIT) Preparation of Investigational Products (IP)

Costs and performance of multicentre, multinational clinical studies are dependent, among other things, on the anticipation of patient recruitment per site and per country, and the total amount amount of study medication which will be needed throughout the study. Experience shows that the original planning often does not match the reality, either due to a surplus of medication being produced on the one hand, or frequent additional supplies being necessary on the other, for example due to additional countries being added to the study. A rather simple process may help to reduce expensive surplus supplies of study medication and allow adaptive planning from the beginning of the study: Just-In-Time (JIT) packaging and labelling.

1.Typical IP manufacturing flow:

The typical flow of IP manufacture requires a thorough planning of amounts, sites and countries, which can be challenging, especially when double-blind crossover designs are applied.

The anticipated amount of study medication packs or patient kits is prepared before the start of the study, and later modifications like addition of countries or change of dosages is no longer possible, or is only possible by considerable additional work.

1.Alternative: JIT packaging and labelling:

JIT packaging and labelling might be an interesting alternative to overcome restrictions caused by, for example, IPs which are limited in their availability and/or very expensive.

Explanations:

- The 1-stage QP release is done against the CTA application and the PSF as usual.
- The shipment order may be country-, centre- and investigator-specific.
- Labelling and secondary packaging / kit packaging is done individually for a specific shipment order.
- The 2-stage QP release is done against the individual shipment order (check for correct labelling and packaging only).

1.Advantages of JIT packaging and labelling

- One batch of immediately packaged IP can be used for several studies at the same time.
- Several batches of bulk IP can be used dependent on their availability (sequential preparation).
- Only study medication already ordered will be prepared.
- Cheap and rapidly-available single-panel labels can be used.
- Label phrases and design may be selected and approved independently and individually per country.
- Label contents may be modified during the study according to adaptations becoming necessary (e.g. use-by date).
- Centre activation of each country can occur independently from the other countries.
- Dose titration can be done during the study without wasting labelled medication.
- Re-supply only limited by the stock of immediately packaged IP.

2.Additional work caused by JIT packaging and labelling

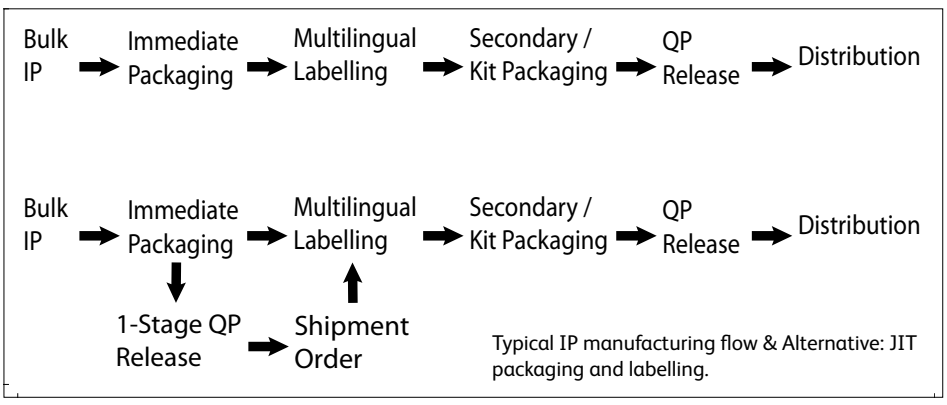
Each shipment order requires a separate labelling and packaging exercise

Each shipment order requires a separate, reduced QP release

3.Conclusion

JIT packaging and labelling is considered to be an attractive alternative for studies with the following characteristics:

- Study to start in each country as soon as the CTA has been received.
- Limited availability of study medication.
- Study medication being very expensive.
- Initial dose titration phase with high variability of final individual doses.
- Additional countries to be included after start of studies which have been supplied with multilingual labelled study medication.
- The manufacturer's QA structure allows for frequent 2-stage QP release.



Typical IP manufacturing flow & Alternative: JIT packaging and labelling.

Dr. Claudio Alexander Lorck, has over 19 years experience in the fields of Quality Control and Clinical Trial Materials Management. Having started his pharmaceutical career at Fujisawa Deutschland GmbH, Claudio now heads the business unit "Clinical Trial Materials" of Temmler Werke GmbH.
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Japan: Open for Business

PEER REVIEWED

Japan has often been regarded as one of the more challenging venues in which to conduct clinical trials and obtain licensing for new medicines, but a host of new initiatives are underway to recast that image.(1,2) Traditionally known as a country with a sophisticated healthcare system but a significant drug-lag,(1) mostly local clinical trials and very few global ones, and harbouring a complex regulatory environment, Japan is now open for business in new and exciting ways.. The country is intent on growing its $81 billion pharmaceutical marketplace, already the world's second largest, by creating a more competitive, transparent, and business-friendly environment that affords more timely Japanese patient access to the latest biopharmaceutical advances. To support this effort, the Japanese government has cited developing a robust clinical trials infrastructure as one of its top priorities.(3)

This article describes how Japan's Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) are building that infrastructure through the implementation of recent guidelines to improve the country's participation in global medicines development and its access to the latest innovations. The changes put forth by PMDA as well as the Japan Medical Association, which has formed a clinical trials network, are creating strong business opportunities for companies anxious to expand their presence in the Japanese marketplace. Although significant challenges remain, this may be the time to weigh them against the opportunities as part of a strategy of moving forward.

Current Status

Within the pharmaceutical sector, Japan is renowned for several key obstacles that have contributed to making it a less than inviting locale for multi-centre clinical trials and medicines approval. Consequently, the country has suffered a well-recognised drug-lag, meaning that drugs come to market in Japan years after they are launched in other countries, such as the United States, the United Kingdom, and Switzerland, for example. Estimates place the average drug-lag in the 2-1/2 to 3-1/2 year range,(1,2) but for some drugs, such as Plavix, the lag was in excess of eight years as compared to its approval date in the US, and for Enbrel, the drug-lag exceeded six years (Table 1).

Drug	US Approval Date	Japan Approval Date	Lag (Years)
Lipitor	December 1996	May 2000	3 yrs 5 mos
Nexium	March 2005	Under development	TBD
Plavix	November 1997	January 2006	8 yrs 2 mos
Advair	August 2000	April 2007	6 yrs 8 mos
Seroquel	September 1997	February 2001	3 yrs 5 mos
Singulair	February 1998	July 2001	3 yrs 5 mos
Enbrel	November 1998	January 2005	6 yrs 2 mos
Neulasta	January 2002	Not Approved	N/A
Actos	July 1999	May 2002	2 yrs 10 mos
Epogen	June 1989	April 2006	16 yrs 10 mos

Table 1: Drug-lag in Japan for 2008's Top Ten Selling Drugs
Source: US FDA; PMDA; PAREXEL analysis.

The main reason for this lag stems from Japan's traditional approach to clinical trials, whereby Japanese studies have seldom been started until after the compound is very far along in clinical development and even registration in other countries. Even after the implementation of ICH Guideline E5 and the introduction of "bridging studies" (i.e. the testing of investigational drugs in Japanese populations to collect pharmacokinetic and pharmacodynamic data to support efficacy, safety, dosage and dose regimen), the extrapolation of foreign clinical data to the Japanese population has not reduced the drug-lag because the bridging approach has been applied relatively late in the development of the new medicine. (4) In order to identify effective and safe dosing in the Japanese, for example, companies have typically waited to see what doses have been found to be safe and efficacious in foreign populations before conducting bridging studies in Japan.

This slow approach, coupled with an evolving regulatory environment and sometimes insufficient adherence to Good Clinical Practice (GCP),(5,6) explains why few multinational clinical trials have been conducted in Japan. Compared to other Asian markets, such as Korea, Taiwan, and Singapore, Japan trails significantly in the number of global trials in which it participates (Figure 1). Further evidence indicates that 93 % of studies conducted in Japan are local, not global, whereas the reverse is true in Taiwan, where local studies account for a modest 16 % of clinical trials, with the remainder being global studies (Figure 2) (7).

Regulatory Changes Bring Improvements

Over the past few years, MHLW and PMDA have become serious about changing Japan's unsatisfactory status in the clinical trial and medicines development arenas. Through a number of initiatives, most notably the guideline *Basic Principles in Global Clinical Trials,(8)* the Japanese agency has started building a competitive infrastructure with the goal of attracting global players and more biopharmaceutical innovation. Published in September 2007, Basic Principles is a guideline designed to increase the number of global clinical trials conducted in Japan and shrink the drug-lag.

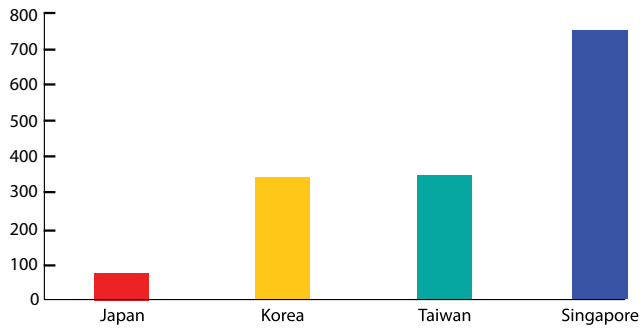

Fig1: Few multinational trials are conducted in Japan vs other Asian markets.

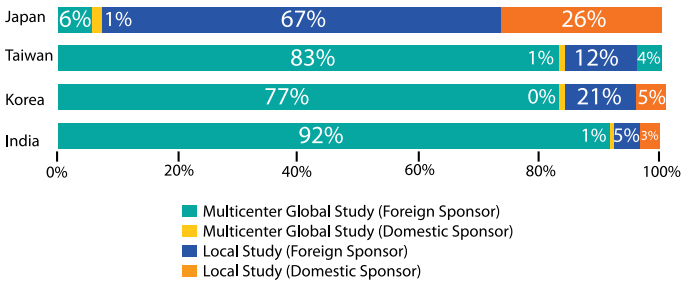

Fig2: Participation of Japan compared to its neighbors.
Source: Basic Principles on Global Clinical Trials

As explained in the guideline, Japan is looking to promote change in drug development strategies by entering the clinical trial process from an early stage of drug development. Specifically, there is an acknowledgement by PMDA that "synchronizing drug development timings in Japan with those of other countries" is essential for eliminating the drug-lag. This entails moving toward simultaneous development of investigational compounds instead of waiting to conduct bridging studies until after other regions have completed substantial portions of their clinical development programmes.

Chart 1: Lists other key aspects of the guideline.

- Improve speed and quality in the approval process.
- Give priority status to companies who approach the Japanese regulators to discuss global clinical trial opportunities.
- Recommend that companies start including Japanese patients in dose-finding studies early in clinical development to identify inter-ethnic differences in dose-response relationships.
- Encourage companies to recruit sufficient numbers of Japanese subjects.
- Allow for appropriate safety evaluation during clinical trials and expanded post-marketing approval studies to gather additional safety information.
- Standardise the collecting and assessing of adverse event information as much as possible across all regions.

In conjunction with Basic Principles are other PMDA efforts to boost global competitiveness, namely the launching of the Five Year

CTC Category	Cases
Anti-Cancer Drugs	66
Cardiovascular Drugs	60
Central / Peripheral Nervous System Drugs	40
Respiratory Tract Drugs	31
Gastrointestinal Drugs	28
Hormone Drugs	23
Antibacterial Agents	22
Drugs for Urogential System	15
Biological Products	11
Bio-CMC	8
Blood Products	5
Radiopharmaceuticals	2
Cellular and Tissue derived products	1
Total	312

Table 2: Number of face-to-face consultation by category of clinical trial consultations conducted in FY 2008.

Standard Review*	FY2006	FY2007	FY2008	End of Sept 2009
Number of Approvals	29	53	53	45
Regulatory Review Time (months)	12.8	12.9	11.3	10.5
Total Regulatory Review Time in Months (regulatory + applicant)	20.3	20.7	22.0	19.0

Table 3: Improvements in PMDA's Performance
Standard review as opposed to Priority Review
Source: PMDA, March 2010

Plan (9) and establishment of the Office of International Programs (OIP) (10). The objective of the Five Year Plan is to improve the conduct of clinical trials and the trial environment, and accelerate regulatory review. OIP, with its orientation toward improving PMDA's international activities, seeks to promote international harmonisation and leverage resources. A recent example occurred in early 2010, when OIP sent a liaison officer to FDA to improve communications between the US Agency and PMDA (11).

Complementing these activities is the Japan Medical Association Center for Clinical Trials (JMACCT), which oversees the Massive Network for Clinical Trials. With funding from the MHLW, the Massive Network is a nationwide network of hospitals and clinics that supports establishing the infrastructure needed to conduct high-quality clinical trials. (12)

This array of initiatives is credited with jump-starting Japan's global standing as a viable clinical trials venue. In November 2009, PMDA presented metrics of its early success at the first China Annual Meeting of the Drug Information Association (DIA)(13), starting with data documenting an increase in global clinical trials that now include Japan. The percentage of Japanese Clinical Trial Notifications (CTNs) – analogous to U.S. investigational new drug (IND) applications – that include multi-regional randomised clinical trials rose from less than 5% in late 2007 to nearly 20% by mid-2009. To continue these improvements, PMDA has been expanding the number of reviewers available for Clinical Trials Consultation (CTC), growing the ranks from 280 in early 2008 to more than 440 by the end of Q1 2010. (14) The number of sponsor-PMDA consultations has jumped from 300 in 2006 (pre-Basic Principles) to an anticipated 1200 by March 2012, (12) and the waiting period to meet with PMDA for a consultation has shrunk from three months (pre-Basic Principles) to two months by March 2009.12 PMDA is actively encouraging sponsors to schedule CTCs where proposed drug development programmes and clinical trial designs can be discussed and agreed with the Agency, and quickly documented in official CTC minutes that are binding on both parties. The rising number of CTCs since 2007 indicates that sponsors are rising to the opportunity and that PMDA is making its reviewers accessible to sponsors. For example, Table 2 (PMDA data) shows the number of CTCs conducted in FY 2008 by therapeutic area, and reflects a significant number of sponsor-PMDA interactions across a wide therapeutic spectrum.

Other measurable improvements, including the rise in the number of drug approvals and the decline in the length of regulatory review time, appear in Table 3 (15).

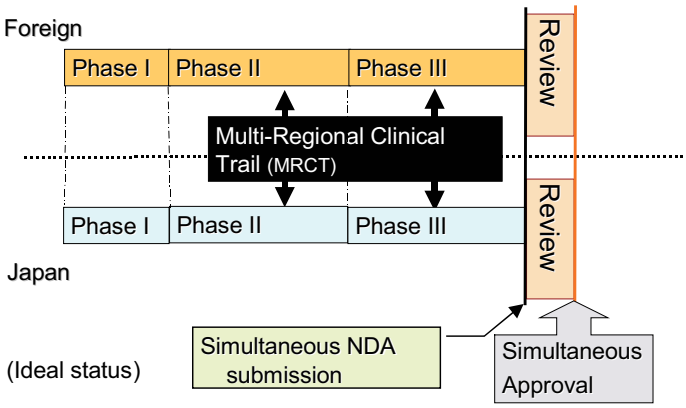

Fig3: Clinical development: global simultaneous development model. Source: Min Yue

Challenges and Opportunities

Amidst the positive outcomes of the efforts by PMDA and the Japan Medical Association, there are a series of challenges that companies face as they attempt to conduct global clinical trials in Japan. Most of the challenges stem from the fact that the changes are recent and Japan's regulatory infrastructure remains relatively understaffed compared to its Western counterparts. Furthermore, the environment for conducting clinical trials in Japan is complex, but within the challenges lie the seeds of opportunities to access the world's second largest pharmaceuticals market more rapidly than has traditionally been the case.

What makes the environment so complex? For starters, all official documents and communications with PMDA, as well as meetings with regulators, must be in the Japanese language, (16) making translators a must. In addition, the Japanese clinical trial environment is relatively bureaucratic, not unlike that in other countries such as the United States. For example, up to 150 essential documents are required as part of good laboratory practice (GLP) paperwork.(2 Thirdly, cultural preferences remain and cannot be rapidly erased by the issuance of a guideline; sponsors must always be prepared to adapt to and work with those preferences – chief among them a Japanese concern for safe dosing, which may differ from Western dosing.

Much of the focus in Japan now is on addressing the drug-lag. Its roots are in the inter-ethnic differences in dose response between Japanese and Caucasian populations. Japanese patients are in some cases treated with a substantially lower dose than what is typical for Caucasians. In order to inform prudent regulatory decision-making, pharmacokinetic (PK) studies have typically been carried out in Japanese populations as part of the drug approval process in Japan.2 But now the opportunity to reduce the drug-lag comes from working with Japanese regulators early, either to launch bridging trials in Japan much sooner, or ideally, to include Japanese patients in multinational clinical trials to attempt simultaneous drug approval in all major markets (Figure 3).

A recent opportunity for sponsors is the fact that Japan is in the early stages of a tripartite effort with China and Korea to lay out objectives and rules as to how clinical trials could be conducted more uniformly amongst these three nations, potentially resulting in mutual acceptance of clinical data.(18) PMDA is actively promoting this initiative, along with the Chinese SFDA and Korean KFDA. They have formed a Working Group and will be carrying out the Joint Research Project on Ethnic Factors in Clinical Data to encourage global clinical trials, and to share clinical data and information on ethnic factors across East Asia. The opportunity for sponsors is to agree a regional clinical trial design through advance consultation with the Japanese, Chinese and Korean authorities, and to conduct the trial with relative assurance that the data collected from Japanese, Chinese and Korean patients will be acceptable to the authorities of all three countries – and potentially at a lower overall cost.

Moving Forward

Japan is stepping up efforts to implement the changes needed to reduce the drug-lag and increase the number of global clinical trials conducted in this populous nation. With the Basic Principles guideline in place, along with the Five Year Plan and the Office of International Programs, PMDA continues to expand its staff, provide them with training, grow the number of CTCs, and overall, increase transparency and flexibility. The regulatory environment remains complex, linked to an evolving infrastructure and issues related to inter-ethnic differences in how compounds perform in the Japanese population. But MHLW and PMDA are dedicated to greater participation in global clinical trials, and are taking the steps needed to achieve this goal. As the Japanese Government has now laid the groundwork, forward-thinking companies can take advantage of these developments by coming to the PMDA table with an understanding of the regulations, challenges, opportunities and culture to increase their chances for successful entry into the Japanese market. Specifically, companies can take advantage of PMDA's openness to CTCs with sponsors to present their global development programmes, propose the inclusion of Japanese patients in clinical trials from an early stage, and negotiate with PMDA a drug development programme that is mutually acceptable. The opportunity exists now. ●

LATE BREAKING NEWS: On May 10, 2010(19) an MHLW official announced that it is set to ask pharmaceutical makers to submit applications to market a total of 109 drugs that have already been approved in other countries. Those medicines are among the 374 drugs that the Ministry has identified as being eligible for a fast-track review process, and some are orphan drugs sought by patients suffering from a rare illness. The 100-plus drugs were recommended by experts in academia or patient groups in light of the seriousness of illnesses for which effective pharmaceuticals are either not available or are very limited, according to the official. The drugs were also chosen for efficacy. A special Ministry task force has pinpointed drugs aimed at illnesses for which treatments are not available in Japan, medicines that have been shown through US or European clinical trials as being superior to existing Japanese treatments in terms of efficacy and safety, and products used in the US and Europe as standard treatment. By the end of the year, the ministry plans to urge manufacturers to submit applications for the remainder of the 374 drugs. Drug makers urged to submit applications by the Ministry starting the week of May 16, will be asked to start clinical trials in Japan within one year; when overseas trial data is available, drug makers would be asked to submit that data to the task force within half a year, according to the MHLW official.

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Alberto Grignolo, Ph.D. is a Corporate Vice President at PAREXEL Consulting. He is now responsible for the organization's Global Strategy and Services, including global registration strategies, worldwide clinical trial applications and marketing submissions, and scientific and technical expert advisory services for bio/pharmaceutical and medical device client companies, with a particular focus on Asia Pacific, Latin America and other emerging markets.

Yoshitaka Aida, DVM, PhD is Director, PAREXEL Consulting, Japan where he assists companies based both outside and inside Japan to develop and commercialize biopharmaceutical and medical device products for the Japanese market. Dr. Aida's areas of specialization include Regulatory Affairs, Drug Safety, Pharmacology, Toxicology, Drug Metabolism, Formulation and Chemical Analysis.

Pharmacovigilance Outlook: Improving Drug Safety Monitoring, Evaluation and Risk Management

PEER REVIEWED

The importance of pharmacovigilance cannot be discounted in its contribution to the prevention of adverse effects of medicines. Since the first introduction of international pharmacovigilance systems in the 1960s, requirements have been evolving to recognise and assess possible safety issues. In addition, the need to promote the ability of pharmacovigilance systems to support the safe and effective use of medicines is increasing.

Multiple factors contribute to the trends we are seeing in global pharmacovigilance today. The speed at which new drugs are introduced into the pharmaceutical market is such that extensive exposure to new medicine in a brief period of time enhances the need for effective systems that can rapidly discover and control potential safety issues. In addition, careful monitoring of new, innovative products is required for those that have unknown safety profiles. These include, for example, products based on new technologies, such as gene therapy and biologics, and those that work through mechanisms of action previously untested on humans or which act on novel targets. In this information age, public awareness is heightened and expectations have been raised regarding safety of medicines, fed by recent high profile safety issues and product withdrawals. As is often the case, the large costs connected with drug safety are a significant factor. This affects both pharmaceutical companies eager to cut short the research on products with an objectionable risk-benefit profile as soon as possible, in addition to the public health cost, with 5% of European Union (EU) hospital admissions estimated to be due to an adverse drug reaction (1).

Undoubtedly, individuals gain in their health and wellbeing by the research into the development of new, effective medicinal products. Yet, the need to efficiently monitor and perform on safety issues involved with pharmaceuticals necessitates that pharmacovigilance systems improve to ultimately enhance their involvement in public health. In this commentary on the state of pharmacovigilance, we aim to cover the current trends affecting the development of pharmacovigilance strategies needed to accomplish this goal.

Integrated Pharmacovigilance throughout Product Lifecycle

Traditionally, pharmacovigilance has focused mainly on post-marketing safety surveillance. However, there has been a shift in recent years towards systematic pharmacovigilance throughout the product lifecycle, as recommended by the CIOMS V Working Group (2).

Whilst acknowledging that the post-marketing use of products will involve exposure of a large number of patients and thus may demonstrate previously unseen, rarer adverse drug reactions, there is still a lot to learn about potential risks in the clinical trial stage, as well as from pre-clinical studies. The benefit of preparing a Development Risk Management Plan (DRMP) and evaluating clinical trial safety data on an ongoing basis is becoming more apparent and is discussed further in later sections.

To prove effective, pharmacovigilance systems need to integrate input from all stakeholders, both within an organisation and externally. The stakeholders within an organisation are many and diverse, as illustrated in Figure 1. These include the Clinical Operations, Clinical Data Management (CDM) and Statistics teams, with their role in running clinical trials and managing and evaluating clinical trial data. Regulatory Affairs, Medical Writing and Public Relations have a key role in the implementation of labelling updates and communication of safety information. Pharmacovigilance should be a consideration right up to board level, to ensure that corporate policies and procedures facilitate the oversight and management of the safety of products and allow escalation of issues quickly and effectively if required. A further important consideration is that many of these activities may be handled by affiliate or partner companies, or outsourced to one or more Contract Research Organisations (CROs). These parties also require involvement to provide a clearly documented, coherent, lifecycle pharmacovigilance system; comprehensive Safety Data Exchange Agreements (SDEAs) can ensure this. The Quality Assurance (QA) department also has a key role in the auditing of the entire pharmacovigilance system (including affiliate and partner companies, CROs and other third parties) to ensure that suitable processes are in place and are followed to a high standard. Lastly, oversight of the entire pharmacovigilance system is required, for example by the EU Qualified Person for Pharmacovigilance (QPPV), if appointed. A Company Safety Committee or similar, comprised of representatives from each function relevant to pharmacovigilance, can also be established to coordinate activities, review all required information and agree on required actions and their communication to relevant parties.

From the regulatory perspective, plans to implement the Development Safety Update Report (DSUR) should serve to harmonise clinical safety reporting across ICH regions, in addition to coordinating safety reporting across the product lifecycle, through its overlap with the Periodic Safety Update Report (PSUR).

Safety Data Management & Evaluation

It is a growing challenge for pharmaceutical companies to manage the large amounts of safety data from numerous sources. The volume is increasing with the conduct of more global clinical trials and post-marketing studies. This will intensify if the proposals to strengthen consumer reporting in the EU are implemented, making it a requirement to report to the regulatory authorities adverse drug reactions received directly from consumers, as is already required in the United States of America (USA). In addition to the increased volume of case safety data that this would generate, there would also be the need for additional follow-up to ensure report accuracy and quality. For smaller Phase I and II studies, a paper-based system

and spreadsheet may prove sufficient for safety data management. However, as the case volume increases, a validated, regulatory compliant safety database may become necessary.

The requirement for unblinding of Suspected Unexpected Serious Adverse Reactions (SUSARs) prior to reporting to EU competent authorities and Ethics Committees necessitates careful planning and safety data management. To maintain the integrity of the trial, companies must decide which personnel will have access to unblinded data (such as members of the Pharmacovigilance Group) and who will not be permitted access (such as clinical and biostatistics personnel involved with the conduct and analysis of the trial). Guidance also suggests that investigators should be kept blinded, which adds to the challenge, particularly for the preparation and submission of periodic reports. Technological advancements do facilitate the management of unblinded data, with the ability to store password protected unblinded data on the safety database. However, definition and documentation of the blinded and unblinded team and processes to maintain these are also helpful.

Sponsors and Marketing Authorisation Holders are increasingly looking for ways to systematically review safety data and perform signal detection and evaluation on an ongoing basis. The use of Data Safety Monitoring Boards (DSMBs) for the monitoring and assessment of data during clinical trials is increasing due to its provision of unbiased review, which may be unblinded without affecting the trial integrity. One consideration is the inclusion of members with knowledge of areas associated with potential risks, in addition to the therapeutic indication of the product.

The value to the Pharmacovigilance department of involving data management and statistics expertise in safety data management and evaluation is becoming apparent. Formal signal detection methodologies using statistical techniques adapted from manufacturing (such as sequential probability ratio test (SPRT) or graphical techniques such as cumulative sum charts (CUSUM)) or data mining approaches (such as proportional reporting ratio (PRR) or Bayesian confidence propagation neural network (BCPNN)) are generally applied to large post-marketing surveillance databases. The volume of safety data within a licence application may be such that a subset of such graphical or statistical techniques could be applied to support the medical review and evaluation. The eagerly awaited CIOMS VIII guidelines on signal detection should also provide some further pragmatic solutions and guidance for effective signal detection.

With safety data being received from numerous sources and held on different clinical and safety databases, effective data flow and reconciliation is vital to ensure the integrity of the databases, as outlined in Figure 2. This must work across all groups handling safety data, be they from within the organisation or CROs. Also, there is a requirement for integration of data for analysis and evaluation and inclusion in documents such as the Integrated Summary of Safety (ISS) for a New Drug Application (NDA). This requires pooling of Adverse Event (AE) data across studies. Careful consideration should be given to ensure biases are not introduced by inappropriate pooling, such as different treatment regimens or differing lengths of treatment.

Centralisation of Case Report Form (CRF) and safety data provides efficiencies and facilitates a high quality global safety database.

There are also proposals to strengthen safety data collection by regulators, with proposed revisions to the EU legislation to make the EudraVigilance database the single point of receipt of Individual Case Safety Reports within the community. The United States Food and Drug Administration (FDA) are also proposing to amend post-marketing safety reporting regulations, to make electronic safety reporting mandatory.

Transparency & Communication

Public awareness and expectations with regards to the safety of products are increasing, as are the demands on companies and regulators for transparency, with effective and timely communication of drug safety issues. The aim is to enable healthcare professionals and consumers to make informed decisions about medicines prescribed and to promote the effective and safe use of those medicines.

Transparency and communication will be best served through gaining input from all external stakeholders in pharmacovigilance. Proposed changes to pharmacovigilance EU legislation (Regulation 726/2004 and Directive 2001/83/EC) are currently being developed in consultation with stakeholders, including pharmaceutical companies, Regulatory Authorities, Health Care Professionals (HCPs) and consumers. As discussed above, these proposed changes would strengthen consumer reporting, which is a positive step towards involving consumers more in pharmacovigilance.

In terms of communication of safety issues and advice on the use of medicines, the proposed changes to EU legislation seek to introduce an EU web portal, which would be the main platform for announcements related to medicinal safety and would include links to member state web portals. EU proposals also suggest changes to the product labelling, both Summary of Product Characteristics (SPC) and Patient Information Leaflet (PIL), to make clearer any information concerning the correct use of medicines. Companies also need to consider education on prescribing use, in addition to the monitoring of the use of medicines to identify any issues with the product name, labelling, packaging or use that may contribute to medication errors. Furthermore, companies require clear processes for the effective communication of changes to the risk-benefit profile of their products.

Proactive Risk Management

The over-arching trend is towards proactive risk management. Pharmacovigilance systems are therefore designed to deliver the key elements of an effective risk management system. These are risk identification, risk evaluation, development of risk minimisation / mitigation strategies and the communication of those strategies to all relevant parties.

The EU regulatory changes referenced previously are designed to promote proactive risk management. Current EU requirements dictate that a Risk Management Plan (RMP) may be required at the time of the Marketing Authorisation Application (MAA) if considered appropriate; however, there is no legal basis for Competent Authorities to request an RMP. The proposed changes to EU regulations would make an RMP a requirement for MAAs for all new active substances. Furthermore, under the proposals, EU PSURs would have a greater emphasis on risk-benefit, with the frequency of the PSUR being specified in the Marketing Authorisation (MA), dependent upon the risk/benefit profile of the medicine.

Summary

Pharmacovigilance has a vital part to play in public health. Pharmacovigilance systems must evolve to meet the changing demands and challenges to continually strive to be effective in quickly detecting and minimising risks, even for previously unexpected or inexplicable adverse drug reactions. Indeed, a primary mechanism by which Thalidomide causes birth defects was only discovered recently (3), nearly fifty years after the link was first made. Current trends see a shift towards integrated pharmacovigilance throughout the product lifecycle, involving input from all stakeholders both within and external to the pharmaceutical company. Sponsors, marketing authorisation holders and regulators are endeavouring to meet the challenges posed by ongoing management and evaluation of safety data, consolidating and integrating data from different sources and carrying out systematic signal detection and evaluation. With the increasing demand for transparency, communication of potential safety issues, risk minimisation strategies and the correct prescribing and use of medicines is also important. The challenges are great and there is no quick solution, but by focusing on these key aspects, pharmacovigilance systems can be improved to allow more effective management of the risk-benefit profile of medicinal products. Achieving such systems will enable us to move closer to the ultimate shared goal of the delivery of the safest and most effective medicines possible, to maximise their contribution to public health. ●

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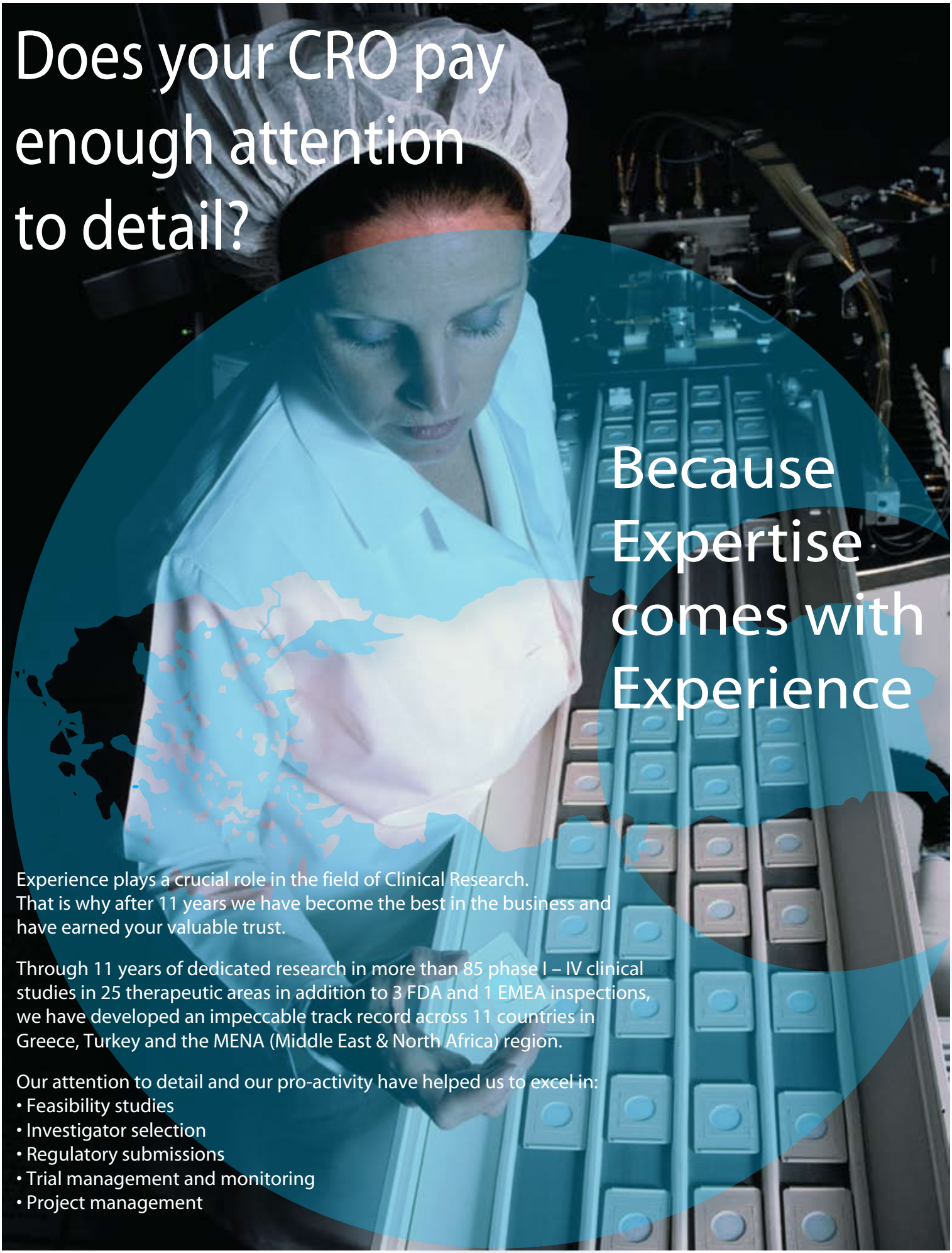
Alison Bond is Head of Pharmacovigilance at Quanticate, leading its team offering complete clinical trial and post-marketing pharmacovigilance services. Alison has worked in the field of pharmacovigilance for nearly 10 years, both within the CRO sector and as an independent consultant. In these roles, Alison has created and managed global pharmacovigilance systems for a number of pharmaceutical and biotech companies, through all phases of clinical development and post-marketing. Alison also led the UK team of drug safety scientists for a global CRO and helped to develop and improve systems and processes for their global pharmacovigilance services. She gained a PhD in the field of rheumatology and has nine years of pre-clinical research experience.

Email: Alison.Bond@Quanticate.com

Katherine Hutchinson is Head of Consultancy at Quanticate. She has been working as a statistician in the pharmaceutical industry for over 20 years, firstly as a statistician in some of the large pharmaceutical companies, and latterly as a senior manager and consultant within the CRO sector. She gained her MSc in Applied Statistics in 1994 and Chartered Statistician status in 2001. Katherine is a Director on the Board for Statisticians in the Pharmaceutical Industry (PSI).

Email: Katherine.Hutchinson@Quanticate.com



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Potential of Middle East and North Africa in Clinical Trials

The Middle East has evolved as a hub for clinical trials over the last five years. There are 31,309 clinical trials currently ongoing globally, and the MENA region accounts for 5% of them (1715 trials). Over the last few decades rapid development has taken place in the MENA region, and pharma companies are investing there in clinical trials. In the Federal Register, Vol. 68, No. 20 (January 30, 2003), the FDA announced the 'Draft Guidance for industry on the Collection of Race and Ethnicity Data in Clinical Trials for FDA Regulated Products'. This indicates the importance of multi-ethnic data.

Though limited information is available on the Arab ethnic population, of late many studies have been published in peer-reviewed journals. This emerging market now holds much potential for clinical trials. ClinTec International is a CRO that has acknowledged this potential, and established its clinical research services in the MENA region approximately five years ago. The registration of three offices in the MENA, namely in the United Arab Emirates (UAE), Lebanon and Egypt, consolidates the growing presence of ClinTec in the MENA region, and is a firm indication of its commitment to propagate clinical research in this region.

It is true that the MENA region spends more than $30 billion on patients suffering from hereditary disease. Thalassemia is a disease prevalent in this region due to the high number of consanguineous marriages. Initiatives have been undertaken by several government bodies to keep a check on thalassemia by offering premarital screening and efficient services to those already affected.

Haemoglobinopathies, glucose-6-phosphate dehydrogenase deficiency, different congenital malformations caused by recessive genes, and several metabolic disorders are prevalent in the MENA region. The Catalogue for Transmission Genetics in Arabs (CTGA) contains a database of genetic disorders that has been reported from the Arab world.

The World Health Organization (WHO) has declared UAE as having the second highest diabetes rate in the world. Hypertension and high cholesterol closely follow. Seasonal and perennial allergic rhinitis are the commonly reported inhalant allergic conditions in these regions. Environmental factors like sedentary lifestyles, ongoing dynamic construction work and frequent sandstorms play a significant role in increasing the susceptibility of an individual to a disease.

However the MENA region boasts hospitals with good infrastructure. The main healthcare providers in these regions are the Ministries of Health (MoH), which provide a highly efficient healthcare system, which effectively and competently utilises the financial resources available to it.

In the past few years, the doctors have gained experience in clinical trials and this region has opened up to clinical research. With adequate training it is expected that the potential of this region will far surpass expectations. IRBs are keen to be trained on how to conduct their proceedings in accordance with international guidelines. All this, together with the pharma industry looking to

invest in clinical trials, makes this a region which holds the promise of long term growth in the area of clinical research.

Some therapeutic areas which have attracted clinical trials are endocrinology, especially diabetes mellitus, CVS, GI, oncology and metabolic disorders. Phase I trials which are designed primarily to evaluate safety and tolerability of the drug in healthy volunteers are not conducted within most of the MENA region, as a majority of the regulatory agencies / ethics committees in the region do not give approvals for Phase I trials. Phase II trials are reviewed and approved on a case by case basis. Phase III and Phase IV are the most common trials conducted in the MENA region. Obtaining clinical trial approvals in the MENA region is a complex procedure, as each

country has a different requirement. Most Gulf countries require only the ethics committee's approval for the conduct of the trials. An approval is required in some countries from the MoH / competent authority. Most recently there has been a rapid change of prevailing regulations and some of the Gulf countries are currently witnessing the implementation of new clinical trial regulations.

However, regulatory experts like ClinTec International with adequate experience in the region, based on the current clinical trial regulations have developed detailed procedures for obtaining clinical trial approvals in this region to help navigate through the maze of requirements. Though the prevailing laws are subject to change, these SOPs / regulatory binders that ClinTec has put together contain a wealth of information and describe the entire procedure of obtaining clinical trial approvals in the MENA regions.

Data generated locally through clinical studies in the MENA region is valuable as pharmaceutical companies use this information in the local population to successfully market their products. Communicating local trial findings to doctors adds significant value to the product, as they can help establish the safety and efficacy of the drug in the local population. Local trials also support regulatory submissions as it is one of the requirements of the FDA to have multi-ethnic data when filing for approvals. The Middle East and North Africa have a wealth of untapped information that is unique and complex to each region. The ethnic profile of the MENA region contributes towards attaining proportional representation of ethnic minorities in trials.

There has been a steady increase in the number of clinical trials in the MENA region, and in a few years' time there will be a boom in clinical trials in this region. Speeding up of regulatory reforms in the MENA, and widening of training and experience are the reasons for this prediction. Pharmaceutical and biopharmaceutical companies have recognised the opportunities and advantages that co-exist with conducting clinical trials in the complex MENA region and are turning to the emerging markets, where long term growth can be sustained. ●

Rani Abraham, is ClinTec's Regional Manager for the MENA region bringing with her over 13 years experience in the clinical research field. Rani has strong experience in both Regulatory and Ethics submissions in the Middle East, with experience in writing SOPs for both the Institutional Ethics Committees and CRO's. She has worked on multiple multinational trials across a variety of indications and therapeutic areas including Cardiology, Psychiatry, and Endocrinology. Prior to joining to ClinTec, Rani worked as a CRA for Global pharmaceutical companies and as a Medical Research Co-ordinator for the Dubai Health Authority as a member of the Medical Research Ethics Committee and holds a certificate in GCP from the Thrombosis Research Institute, London.Rani gained her Masters in Pharmacy, majoring in Immunopharmacology and Cancer Chemotherapy from the MAHE University, India and is a member of the Pharmacy Council of the state of Kerala.

Email: rabraham@clintec.com

Evaluating the Cognitive Effects of Antiepileptic Treatment in Children with Epilepsy

PEER REVIEWED

Cognition in Children with Epilepsy

Epilepsy is among the most common neurological disorders in the world, with prevalence exhibiting two peaks at the extremes of life, in childhood and in the elderly. Population-based studies report a prevalence rate of epilepsy in childhood of 3.6 to 4.2 per 1000 in developed countries (1,2) rising to twice these figures in developing countries (3,4).

It is well known that epilepsy can be associated with a variable degree of cognitive impairment (5,6,7). This is of special concern in children where learning abilities can be affected, leading to long-term effects on academic achievements as well as on social interactions and quality of life of the subjects(8,9,10,11).

Several studies and surveys have shown that the most frequent cognitive disabilities are attention and concentration impairment, and difficulty in performing complex tasks, with a slowing of the information processing speed (12,13,14,15). Several etiological factors can be identified (16,17) so that each individual case requires a careful evaluation of the subject and his/her family and social environment. The main causal factors to be considered are the underlying brain pathology; the type of epilepsy, and the characteristics of seizures, in terms of frequency, severity and type (e.g. simple or complex or generalised); the age of epilepsy onset; the use of antiepileptic drugs; and finally the familial and sociocultural environment (18,19,20,21,22).

All these factors can contribute in different ways and with different weights in determining the child's cognitive impairment. Usually children with uncomplicated idiopathic epilepsy do not suffer from cognitive impairment, which is more frequent in symptomatic epilepsy (22,25). Almost all studies conducted so far confirm that early age of onset is a strong predictor of cognitive impairment; this apparently being related not only to the symptomatic nature of epilepsy or to the presence of encephalopathy (22) in young children but also to the young age itself. A frequent occurrence of subclinical epileptiform discharges, even in subjects apparently seizure-free, also seems to contribute to cognitive and learning difficulty (24,25,26,27).

Antiepileptic Drugs (AEDs) and Cognition

The role of the AEDs in this complex and multiform situation is difficult to define, and it can be further confounded by the fact that AEDs can alter the brain function and hence the mental processes, whilst at the same time they can improve the epileptic condition with a potential positive effect on cognitive functions (28). AEDs might interfere with cognitive function by the same mechanism by which they act on seizures (28). But for many AEDs the mechanism of action on the brain is only partly known, therefore it cannot be ruled out that they interfere with mental processing by different mechanisms of action. Cognitive side effects of "older" AEDs in adults generally, are well established, with phenobarbital and traditional benzodiazepines presenting the highest risk for cognitive impairment (29,30,31). Other AEDs, like carbamazepine, phenytoin or valproate, have generally comparable cognitive profiles, with modest psychomotor slowing (31,32,33,34,35,36,37). More recent AEDs (e.g., gabapentin, lamotrigine, levetiracetam, tiagabine and oxcarbazepine) are thought to have milder, if any, cognitive side effects (38,39,40,41,42,43,44). Among the newer AEDs, only with topiramate have more pronounced cognitive effects been demonstrated and only in adult subjects, particularly if topiramate is initiated quickly and with high doses (45,46,47,48).

Over the past two decades the number of AEDs has dramatically increased with a consequent increase in the possible combinations, favoured by the reduced risk of pharmacokinetic interactions among different AEDs as well as by the better safety profile of newer AEDs. Polytherapy in epilepsy has become frequent in pharmacoresistant subjects, which still represent a considerable proportion of adults and children with epilepsy. This obviously may increase the risk for developing cognitive impairments.

Blaming AEDs for adverse effects on cognition or on attention and memory is somewhat easy, based particularly on the unfavourable safety profile of some old AEDs, but this can be sometimes misleading. Other factors that can influence the cognitive abilities of children might be overlooked, for example, the behavioural and social problems that these children encounter because of their illness and the impact on intellectual competences are not always paid the deserved attention.

Several studies have tried to evaluate the specific role of different AEDs in determining cognitive impairment in either adults or children. However, most of these studies suffer from methodological flaws, such as poor patient selection, including subjects of different ages with different types and/or duration of seizures (16,31). The statistical design is also often poor, with too small sample sizes and lack of adequate statistical power, inadequate or missing control group (49), and lack of definition of a clinically significant effect when evaluating different aspects of cognition.

An additional issue is the kind of tests used to evaluate the potential cognitive impairment and the practical effects of these tests when following children over a period of time. A parallel control group with similar characteristics would be of paramount importance, but sometimes difficult to obtain in practice.

Vermeulen (49) in a very comprehensive review described and commented in great detail on all possible methodological flaws of the different study designs used to evalute the effects of AEDs on cognition. Of the 90 investigations he retrieved and evaluated, he restricted his final assessment to only 10 clinical trials on initiation monotherapy, with control group data and acceptable repeated measures. Of these, only four trials were conducted in children. One of the main issues of these trials was that a wide variety of assessment tools had been used to search for cognitive effects of AEDs, ranging

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from measurements of reaction time and motor speed to intelligence tests. Some of these measures may be more sensitive to drug-induced changes in cognition than others. Furthermore, the majority of the studies were designed to find large treatment effects, hence the small sample sizes, while it is likely that the cognitive profiles of different AEDs are characterised by limited treatment effects. Therefore, the author could not draw any reliable conclusion on the effects of AEDs on cognition or on differential effects among AEDs. The situation has not undergone any considerable improvement in more recent investigations. A search conducted via PubMed of articles on randomised controlled trials of cognitive effects of AEDs in children, yielded a total of 32 items. Thirteen of these were excluded as not relevant for this search (febrile convulsions, effects on cognition mentioned only as adverse events, etc). Therefore 19 trials remained to be considered. In some of these, the primary study end point was not a cognitive variable. In the last five years, four multicentre trials conducted only in children with epilepsy assessing the effect of newer AEDs on cognition as primary end point have been published (43,44,50,51). The main characteristics of these trials are illustrated in Table 1.

From Table 1, it can be observed that two trials were conducted with the AED under investigation administered as monotherapy and two trials with the AED as add-on therapy. The type of epilepsy differed among trials as well as the duration of treatment and time interval between baseline testing and re-testing. Two trials used the same neuropsychological test battery (FePsy®), but only one selected a primary variable as primary end point among the several variables composing the test. The number of patients enrolled in each trial ranged from 6151 to 11243 (50), but the study by Pressler et al.(51) had a cross-over design. Therefore, small comparable sample sizes were used, and only in the research by Donati et al.(43) and Levisohn et al.(44) were a formal statistical hypothesis and a sample size calculation performed.

In general, these studies did not show important effects of newer

Table 1: Recently published clinical trials of cognitive effects of AEDs in children with epilepsy.

	Main inclusion criteria	Type of epilepsy	Treatment	Treatment duration to the primary end point	Neuropsychological tests/ questionnaires	Primary end point
Levishon et al. 2009	4-16 y ≥ 1 seizures in the past 4 weeks 1 or 2 concomitant AEDs IQa ≥ 65	Partial-onset seizures	Adjunctive: Levetiracetam	12 weeks	Leiter-R AMb, WRAML-2c, CBCLd, CHQe	Leiter-R AM memory screen composite score
Donati et al. 2007	6-17 y ≥ 2 seizures in the past 4 weeks ≤ 2 secondarily generalised seizures within the past 3 months Newly diagnosed Previously untreated	Partial-onset seizures	Monotherapy: OXCf vs CBZg or VPAh	6 months	FePsy® (computerised test battery), Rey Auditory Verbal Learning Test, Raven's SPMi for children	Computerised Visual Searching Task (from FePsy®, information processing speed)
Kang et al. 2007	5-15 y ≥ 2 partial-onset seizures in the past 6 months Normal intelligence	Benign Rolandic epilepsy	Monotherapy: TPMj vs CBZ	28 weeks	BGTk, KEDI-WISCl (Korean WISC-R), Conners scale, Korean CBCL	A series of summary indices and scores from the used tests and scales
Pressler et al. 2006	7-17 y seizure-free or only occasional seizures not requiring AED adjustments Having some evidence of cognitive impairment IQ ≥ 70	Benign Rolandic epilepsy	Adjunctive: Lamotrigine	8 weeks of stable dosing after titration (at the end of each cross-over phase of treatment)	FePsy® (including 13 variables)	All 13 variables of the FePsy®

aIQ: Intelligence Quotient, **b**Leiter-R AM: Leiter-Revised Attention & Memory, **c**WRAML-2: Wide Range Assessment Memory & Learning-2, **d**CBCL: Child Behavior Checklist, **e**CHQ: Child Health Questionnaire, **f**OXC: oxcarbazepine, **g**CBZ: carbamazepine, **h**VPA: valproate, **i**Raven's SPM: Raven's Standard Progressive Matrices, **j**TPM: topiramate, **k**BGT: Bender Gestalt Test, **l**WISC: Wechsler Intellinge Scale for Children

AEDs on various aspects of cognition, but one may wonder whether the appropriate research methodology was employed and how much the results obtained can be extrapolated to the general population of epileptic children.

Testing Cognitive Function in Epileptic Children

The EMA guidance on clinical investigation of antiepileptic drugs (CHMP/EWP/566/98 Rev. 2), revised in 2010, recommends that, when developing a new AED for paediatric use, "short term and long-term studies should be designed to detect possible impact on brain development, learning, intelligence". A similar concept was expressed in 1981 in the FDA guidance on antiepileptics: "studies designed to test rates of learning and performance shall be included".

Both guidances are quite vague about the kind of tests required, although clear in stating that the evaluation of effects on learning and intelligence should be part of the assessment of AEDs particularly for use in children.

Based on the new European legislation on paediatric medicines, a plan detailing the clinical studies to be performed in the paediatric population is to be submitted and granted approval. Therefore, it is highly likely that proper testing for cognitive effects of AEDs in children will become part of this plan. The timing and kind of testing as well as the most adequate study design could represent a topic of discussion for agreement with the Paediatric Committee of the European Medicinal Agency.

The current situation of uncertainity and lack of standardisation can lead to important differences among trials on AEDs regarding the methodology employed to evaluate cognitive effects, that ultimately do not help the neurologist when selecting the most appropriate AEDs for an epileptic young patient, if he also intends to take into consideration its potential for adversely affecting cognition, besides its efficacy in treating seizures and its safety and tolerance.

Designing a Clinical Trial to Investigate Effects on Cognition

Some of the problems that can be encountered when designing a trial in epileptic children to evaluate AEDs cognitive effects can be summarised in the following questions: AED as adjunctive therapy or as monotherapy? If adjunctive, is there any limitation in the type of concomitant AEDs? Duration of treatment? What kind of tests to use? How to take into account the interference of the antiepileptic effect of the drug?

Ideally, cognitive effects should be evaluated when the AED is taken as monotherapy, possibly in newly diagnosed patients (43). However this design poses some problems: first of all, in the initial stages of clinical development, AEDs are usually investigated as adjunctive therapy, this representing the first approved therapeutic indication, while monotherapy use is evaluated and authorised at a later stage. Therefore, if the effects on cognition need to be assessed early in the development of the drug in children, it is likely that the drug can only be used as add-on therapy. Controlling for the concomitant AEDs can prove difficult and can considerably restrict recruitment capabilities, so that children enrolled in the study may be receiving different classes of AEDs at different doses. The number of concomitant AEDs can, however, be restricted and those drugs that are known to affect cognitive abilities prohibited (e.g. not more than two AEDs allowed, phenobarbital or benzodiazepines prohibited). Stratification by concomitant antiepileptic treatment may help. It should be considered that enrolling children with refractory epilepsy would select a more severely affected patient population with higher chances of neurocognitive impairments.

In order to ethically justify adding a new AED to an existing therapy, children should present with less than optimally treated epilepsy, i.e. they should suffer from some seizures. However, it would be preferable that not many seizures occur at screening, because these may heavily interfere with the cognitive state at baseline and with the one achieved at the end of the treatment, if in the meanwhile the new AED has been successful in relieving from seizures.

An additional problem is represented by the control group: active or placebo? In case of newly diagnosed subjects receiving monotherapy, the control group can only receive an active drug, otherwise some of the children enrolled in the study would be withheld from receiving medical treatment for their illness. A comparison with an AED raises a series of additional problems, like the choice of the comparative AED, what is known of its effects on cognition, etc. In case the trial is designed with the new AED as adjunctive therapy, the control group can receive the placebo on top of the underlying antiepileptic therapy, but this can be done only for a relatively short period of time and if well accepted by study participants and their parents (and the investigators and the ethics committees). It is unlikely that in such a study design the duration of treatment could be longer than 12 weeks. This should be considered when selecting the most appropriate neuropsychological test, to avoid practice effects as a confounding factor.

Evaluating whether an AED can affect the cognitive functions of the child can be regarded as a safety issue and the study then designed as a non-inferiority trial, where the goal is to show that the new drug is at least not worse than either a currently used AED with few or no known effects on cognition or placebo added to underlying therapy. For the non-inferiority trials, defining the delta, i.e. the clinically meaningful difference to use for the statistical hypothesis, remains a big and often unresolved issue. A weak delta definition can invalidate trial results.

Finally, a proper neuropsychological test should be selected. Some of the criteria to be adopted for guiding the selection may include the possibility of reliable re-testing, and the existence of a normative reference database, better if available for children with epilepsy (52,53). Given the multinational nature of the majority of clinical trials, the cultural adaptation of the test to be used becomes an important issue to be considered (53). Depending on the test to be used, validated versions for the countries where the study is to be conducted should be made available. For the choice of the test, it is crucial to decide what the most relevant domains of cognition are that have to be investigated. As mentioned earlier in this article, there is a general agreement that in epileptic children attention, memory and speed of mental processes are mostly affected (12,43,44). Therefore, it may be appropriate to select neuropsychological tests that are designed to specifically detect alterations in these cognitive domains over time. A number of neuropsychological tests and test batteries specifically designed for research purposes in clinical trials have been developed, the most recent ones as computerised versions, that make the administration and the data management much easier and more reliable (52,53). Tests with multiple parallel forms that can be reliably administered repeatedly within a limited time interval should be preferred. Traditional intelligence tests evaluating the subject's IQ, although useful for a baseline and

long-term assessment of the global cognitive condition, can prove inadequate for investigating the effects of AEDs, and not sensitive enough to catch small changes in specific domains (31,52).

Conclusion

With the advent of several newer AEDs and the more recent focus from regulatory agencies on paediatric drug development, there is a growing interest in the potential either negative or positive effects of AEDs on the cognitive function of children with epilepsy. An increase in the number of clinical trials dedicated to the evaluation of such effects is therefore expected in the future. However, no standard methods of assessment are currently available and different tests and study designs are used, with several methodological drawbacks that make the study results not always reliable and difficult to extrapolate to a more general patient population. ●

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Dr. La Noce, is a qualified physician and holds a MD degree from the University of Pisa, Italy. She got a PhD in Neuroscience from the same University and spent nearly 10 years doing research in neurophysiology at the University in Italy and in the UK before joining the pharmaceutical industry. She has been head of neuroscience pre-clinical laboratories in a major Italian Pharmaceutical industry for seven years. She has been subsequently responsible for clinical research in different therapeutic and diagnostic areas for about 10 years in several pharmaceutical and biotech companies, prior to joining PharmaNet Development Group, a global contract research organization, where she is currently covering a position of Senior Medical Director within the global Medical Affairs Group. She is a member of the PharmaNet global Neuroscience Division.

Email: ALaNoce@pharmanet.com

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The Opportunities for Treating the Cognitive Declines which Accompany Normal Ageing

PEER REVIEWED

Cognitive function has long been known to decline with normal ageing, and recent findings indicate that this decline starts in early adulthood. While these declines are recognised, there is currently no regulatory acceptance to encourage the pharmaceutical industry to develop medicines to treat these age-related deteriorations; and the industry is therefore currently focused on Alzheimer's and other dementias, as well as the condition of Mild Cognitive Impairment. Recent surveys have shown that professional groups, students and the military are using 'smart drugs' like modafinil off-label to promote cognitive function, and such use is promoting much controversy, due in part to the safety risks associated with such use. A growing body of data is accumulating showing that naturally occurring substances can enhance cognitive function, even in young volunteers. This provides an alternative strategy for those individuals who wish to optimise their mental performance and to attempt to correct age-related declines by using naturally occurring substances which are more freely available. This paper considers the research findings that could provide a rationale for such self-medication, which must be weighed against the safety risks for healthy individuals.

The Measurement of Cognitive Function

Cognitive function relates to those mental abilities which enable us to conduct the activities of daily living. Many aspects of cognitive function are relatively stable and unaffected by, for example, ageing, fatigue, drugs or trauma; while other aspects such as attention and memory are variable by nature and highly susceptible to change. Tests of cognitive function assess how well various cognitive skills are operating in an individual at any particular time. Such evaluations require individuals to perform tasks which involve one or more cognitive domains. Thus if a researcher wished to assess memory, the test would involve the memorisation of information and the outcome measure would reflect how well such information could be retrieved. Equally, to assess the ability to sustain attention, the test could involve monitoring a source of information in order to detect pre-defined target stimuli over a period of time, and the outcome measures would reflect the speed and accuracy of the detections. It is important to note that the only way to measure cognitive function directly is by assessing the quality of performance on cognitive tests or behavioural tasks. It is of interest to assess how the individual feels about his/her levels of cognitive function, but this is simply supportive evidence for the assessment of task performance. Similarly, various measures of brain activity (for example electroencephalography and fMRI scanning) do not measure the quality of cognitive function directly but rather provide us with independent but nonetheless hugely valuable information about the activation of certain brain areas and the inter-connecting pathways between various areas which are crucial for successful completion of various cognitive operations.

It is important that the researcher in this field identifies the appropriate domain of cognitive function to investigate. While 'cognition enhancement' is an acceptable generic term, as is 'health promoting', both science and regulators require more specific targets, which respect the independence of different domains when considering specific claims. For example, why in medicine would a drug which helped pulmonary function be expected to help the liver? This illustrates the limitation of global scores of cognition for nutritional claims, and should guide researchers to seek assessments of specific target domains of function. There are a number of core cognitive domains which can be evaluated, including attention, information processing, reasoning, memory, motor control, problem solving and executive function. Taking memory as an example, there are four major types: episodic or declarative memory, working memory, semantic memory and procedural memory (see Budson and Price, 2005). As Budson and Price illustrate, relatively few conditions are associated with impairments to semantic memory and procedural memory, while working and episodic memory are impaired in a wide variety of neurological, psychiatric, surgical and medical conditions. This creates a rationale for directing testing towards working and episodic memory as a more fruitful potential area to evaluate in novel conditions, and most test systems recognise this approach. Further, tests specific to particular domains are, when available, ideal, as this helps to facilitate the substantiation of any claims made on the basis of the research findings. The most specific tests are attentional tests, as well designed tests of attention do not require aspects of memory or reasoning for task performance, and thus changes in performance can be relatively clearly attributable to effects on attentional processes. As attention is important for the performance of any task, when seeking to evaluate other domains, it is useful to also assess attention additionally in order that the relative contribution to any effects of changes to attention can be established. Most well established test batteries include assessments of attention, working and episodic memory, motor control, and aspects of executive function.

Automation of Cognitive Tests

Automation of cognitive tests brings numerous advantages (eg Wesnes et al, 1999); the most relevant to the area of cognition enhancement is improving the signal to noise ratio. Noise, ie unwanted variability, is decreased by the standardisation such testing can bring to test administration and the reduction of errors in scoring. However the signal can also be increased due to the extra precision in assessment which millisecond resolution of response times can bring. Furthermore, aspects of cognitive function can be assessed which cannot be measured using traditional pencil and paper measures. Major tests of attention such as simple and choice reaction time have always been automated, as have intensive vigilance tests like the continuous performance test and digit vigilance tasks. Further, computerised tests of verbal and object recognition permit, besides the assessment of the accuracy of recognition, the time actually taken to successfully retrieve the information from memory. This important aspect of memory has been overlooked by traditional tests which cannot make this assessment, but this aspect of memory declines markedly and independently of accuracy with

normal ageing, and is severely compromised in many debilitating diseases such as dementia (eg Simpson et al, 1991; Nicholl et al, 1994; Wesnes et al, 2002). Further in Mild Cognitive Impairment, such slowed speed of retrieval of information is an early characteristic of the disease (Nicholl et al, 1995), which also can respond to pharmacological treatment (Newhouse et al, 2009). Automation also provides the same benefits for tests of the ability to retain information in working memory, as the role of working memory is to facilitate the performance of ongoing tasks; and clearly it is not just the ability to correctly retrieve the information that is important, but also the time taken to retrieve this information; something which cannot be assessed with traditional tests such digit span, and is again something which is impaired in the dementias (McGuinness et al, 2009). A further important benefit of assessing speed is that it permits 'speed-accuracy trade-offs' to be identified, which helps to avoid misinterpretations of study findings.

Cognition Enhancement

A recent definition of cognition enhancement is 'the amplification or extension of core capacities of the mind through improvement or augmentation of internal or external information processing systems' (Bostrom and Sandberg, 2009). Aspects of cognitive function that are targets for enhancement include attention, information processing, memory, planning, reasoning, decision making and motor control. Bostrom and Sandberg argue that an intervention aimed at correcting a specific pathology or defect of a cognitive subsystem may be characterised as therapeutic, while enhancement is an intervention that improves a subsystem in some way other than repairing something that is broken or remedying a specific dysfunction. This distinction is interesting, and accurately characterises the various compounds which are being developed and studied in this rapidly growing field.

Drugs to enhance cognitive function are currently receiving a large amount of public attention and ethical debate (Cakic, 2009), due to their widespread use by students, the military and many professional groups (Sahakian and Morein-Zamir, 2007). In 2008, the journal Nature reported the results of an online poll, in which 20 % of the 1400 respondents admitted that they had used "neuro-enhancers" to stimulate their focus, concentration, or memory (Maher, 2008). While 96 % of respondents felt that individuals with neuropsychiatric disorders who have severe memory and concentration problems should receive such substances, 80 % felt that anyone who wanted one should be allowed, and 69 % said they would take one provided the side-effects were low. The high level of interest can be illustrated by a recent article in The Times Online (Bannerman, 2010) entitled 'Bring smart drugs out of the closet, experts urge Government', and another recent article in Time Magazine entitled 'Popping Smart Pills: The Case for Cognitive Enhancement' (Szalavitz, 2009).

Guidelines for Establishing Cognition Enhancement

Our understanding of cognition enhancement is at an early stage, and there are few, if any, established criteria. For a compound to be established as an enhancer of one or more aspects of cognitive function, the following criteria have been recently proposed (Wesnes, 2010).

1.Improvements must be identified by well recognised and extensively validated tests of cognitive function.

2.Improvements should be to one or more major domains of cognitive function.

3.Improvements must be seen on core measures of task performance, and any suggestions of speed-accuracy trade-offs should be interpreted with caution.

4.Improvements in one cognitive domain should not occur at the cost to another.

5.The improvements should not be followed by rebound declines.

6.The improvements should be of magnitudes which are behaviourally and clinically relevant.

7.The improvements should not be subject to tachyphylaxis over the period for which the treatment is intended to be used.

8.Self-ratings are of interest, and may be used as supportive evidence, but are not sufficient in the absence of objective test results.

Ageing and Cognitive Function

There is a surprising amount of debate about the declines in the quality of mental functioning which accompany ageing. A traditional approach has been to compare young adults (eg 18 to 25 years) to the elderly (eg 65 to 80 years), and much research has shown that a variety of aspects of cognitive functioning are poorer in the elderly. One consistent criticism of this approach is that the elderly group grew up in a different era, which may have limited their subsequent abilities (for example due to socioeconomic factors such as more limited educational abilities and poorer nutrition), and thus the differences may not simply have been due to ageing. A research group based at the University of Virginia, USA, led by Timothy Salthouse, has comprehensively investigated this area over the last few decades. The outcomes of this research programme have been recently summarised (Salthouse, 2010). The approach of Salthouse and colleagues has been to assess thousands of healthy individuals across the age range on a variety of traditional neuropsychological tests and to evaluate the pattern of change by decade from early adulthood until the 80s. The consistent finding has been for linear declines to be present in a range of measures of attention, information processing, reasoning and various aspects of memory from the twenties onwards. Using a variety of analytic techniques, the group have established that despite common assumptions to the contrary, age-related declines in measures of cognitive functioning are relatively large, begin in early adulthood, are evident in several different types of cognitive abilities, and are not always accompanied by increases in between-person variability. This pattern has also been identified over the same age range using computerised tests of cognitive function, showing linear declines in five-year cohorts to the speed and accuracy of various aspects of attention, working and episodic memory (Wesnes, 2003; 2006; Wesnes and Ward, 2000). This effect is illustrated in Figure 1 for choice reaction time and the time taken in memory tasks to decide whether or not information presented has been previously presented. As can be seen, the declines are linear across the age range, starting in the late twenties. Further, for both measures, a decline of one standard deviation can be seen by early middle age, and by at least another by the sixties. An important aspect of the latter findings is that the individuals tested had participated in clinical trials as healthy subjects, and consequently were free of major medical or psychiatric conditions; therefore such declines represent a best case for normal healthy ageing. The same tests have been administered to patients with a variety of conditions including hypertension, heart disease, fibromyalgia, ADHD, epilepsy, narcolepsy, chronic fatigue syndrome, schizophrenia, and multiple sclerosis. When each of these populations is compared to age-matched healthy controls, cognitive deficits of one or more standard deviations are seen on, for example, the ability to focus attention (Wesnes, 2006). This body of research therefore indicates that major aspects of cognitive function decline with normal ageing, and that illness further increases these declines.

In recognition of the cognitive declines in normal ageing, the US National Institute of Mental Health (NIMH) set up a working group in 1986 to agree criteria for the condition of Age-Associated Memory Impairment (AAMI) (Crook et al, 1986). The aims of the criteria were to identify those elderly individuals (50 years and older) who were aware of memory loss that had occurred gradually, who

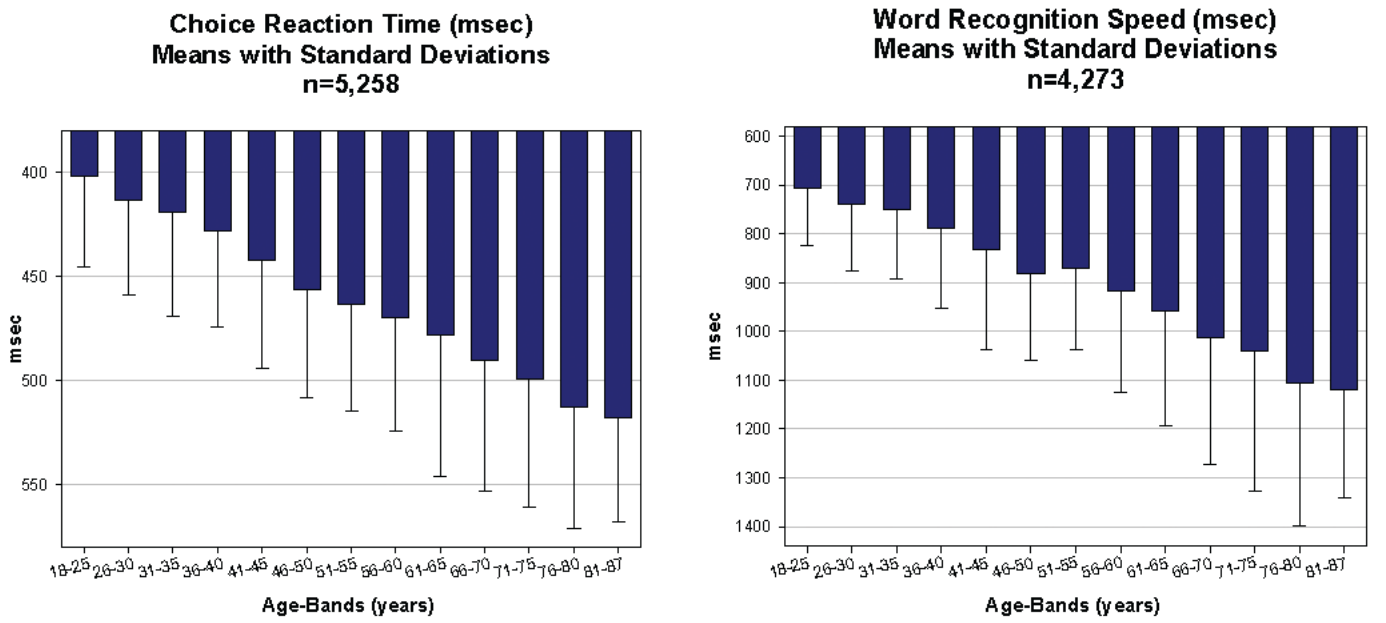

Figure 1: Declines in normal ageing on a test of attention (choice reaction time) and a test assessing the speed of correctly recognising previously presented words.

scored at least one standard deviation below the normal score for that of the young on a widely recognised test of memory (e.g. the Benton Visual Retention Test; the Logical Memory Subtest of the Wechsler Memory Scale, etc.), who showed evidence of adequate intellectual functioning (using the vocabulary subtest of the Wechsler Adult Intelligence Scale), and who showed no evidence of dementia (as assessed by a Mini Mental Status Examination score of 24 or above). The exclusion criteria were designed to exclude those whose poor performance was not due to normal ageing, for example being secondary to disease or actually being dementia. A number of clinical trials subsequently evaluated the effect of various pharmacological and herbal treatments for AAMI, with some limited success (for review see Wesnes and Ward, 2000). The Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM-IV) identified Age-Associated Cognitive Decline (AACD) as a condition which may be a focus of clinical attention (diagnostic code 780.9). The advantage of AACD is that it extended the range of impairments from simply memory to cognitive functioning in general, thus encompassing attention, information processing and a range of other aspects now known to deteriorate with ageing. The definition was for a 'decline in cognitive functioning consequent to the ageing process that is within normal limits given the person's age. Individuals with this condition may report problems remembering names or appointments or may experience difficulty in solving complex problems. This category should be considered only after it has been determined that the cognitive impairment is not attributable to a specific mental disorder or neurological complaint (page 684 DSM-IV). However, regulatory bodies have not accepted AAMI, AACD or other similar conditions as legitimate conditions for drug registration, and much of the focus of drug development in the last decade has moved to the condition of Mild Cognitive Impairment (MCI) (Petersen and Morris, 2005). However, the criteria for an individual to be classified for this condition is to be 1.5 standard deviations poorer than age-matched controls on a recognised test of memory, which limits the condition to less than 10% of the population, which thus has no relevance for the majority of the population who are experiencing age-related cognitive decline. Further, despite some very large clinical trials of potential treatments for MCI, only occasional findings of enhancements have been identified in the condition (eg Newhouse et al, 2009). Part of the problem was that the endpoint of many trials was the rate of conversion to Alzheimer's disease, which required long-term trials with large samples of patients, and the fact that in many trials the expected rate of conversion did not occur in the placebo-treated groups.

Treating Age-Related Cognitive Declines

The reticence of regulatory bodies to accept age-related cognitive declines as a suitable condition for treatment is obviously at odds with current general medical practice which seeks to treat a huge variety of other age-related conditions, ranging from failing hearing and eyesight to hip replacement. In the absence of regulatory acceptance or any consistent pressure from advocate groups, individuals the world over are left alone to seek to attempt to preserve their cognitive abilities as they age through a variety of techniques including physical and mental exercise (eg brain training), as well as with 'smart drugs' mentioned earlier.

Another approach available to individuals who wish to minimise age-related declines in mental efficiency is to seek various natural and nutritional substances which can be obtained 'over the counter'. Certainly there has been a large research effort over recent decades to evaluate the effects of natural therapies upon cognitive functioning. While many naturally occurring plant extracts are commonly misconstrued to be 'safe'; the use in Eastern cultures over millennia of substances such as ginkgo biloba and ginseng has identified the general absence of side-effects of such products. Ginkgo biloba for example has been the subject of enduring worldwide research interest for the last four decades, and a large and generally consistent body of research identifying positive effects on cognitive function has been identified by various research groups in healthy young and elderly volunteers (eg Brautigam et al, 1998; D'Angelo et al, 1986; Kennedy et al, 2000) and mildly cognitively impaired elderly patients (eg Kleijnen and Knipschild, 1992; Rai et al, 1991; Wesnes et al, 1987). While large well-controlled trials have shown the ability of ginkgo to treat the cognitive deficits in patients with Alzheimer's disease and other dementias (eg LeBars et al, 1997; Napryeyenko and Borzenko, 2007), a very large trial has shown that the compound is not able to prevent the development of dementia (DeKoskey et al, 2008); though it has to be acknowledged that none of the registered

treatments for the disease have been demonstrated to do this either. A follow-up publication on the DeKoskey study however showed that gingko did not prevent the rates of cognitive decline over a median six-year period in individuals aged 72 to 96 years (Snitz et al, 2009). On balance, while ginkgo clearly does not prevent cognitive decline in elderly individuals, or prevent the onset of dementia, it does appear to have beneficial cognitive effects on younger populations, and also patients with dementia.

Other research programmes have evaluated the effects of a combination of standardised extracts of ginkgo biloba and panax ginseng, showing improvements to working and episodic memory with acute doses in volunteers (Kennedy et al, 2001; 2002), patients with neurasthenia (Wesnes et al, 1997), and middle-aged volunteers (Wesnes et al, 2000). In each of these four studies, statistically reliable improvements were seen to the ability to successfully hold and retrieve information in short-term (working) and long-term (episodic) memory. There were no improvements to attention, or to the speed with which the information could be retrieved from memory. In the Wesnes et al (2000) study, 256 healthy volunteers with a mean age of 56 years (range 38 to 66) were tested in a 14-week randomised placebo controlled double-blind study, and over the period of the study, an overall improvement in the ability to store and retrieve information in memory of 7.5% was identified. A subsequent analysis of these data showed that the magnitude of the improvement was sufficient to counteract the decline that would have occurred in the population compared to a younger population of 18 to 25 years. This is evidence that age-related cognitive declines can be reversed by natural substances which can be purchased over the counter in pharmacies, and offers individuals the chance to self-medicate with relatively safe substances to maintain cognitive function into late middle age.

While the beneficial effects of caffeine are widely recognised (eg Smit and Rogers, 2000; Smith et al, 2005; Haskell et al, 2005), a range of other naturally occurring substances have been found to improve cognitive function, including pyroglutamic acid (Grioli et al, 1990), phosphatidylserine (Crook et al, 1991), guanfacine (McEntee et al, 1991), huperzine (Wang, 1994; Zangara et al, 2003), ginseng + vitamins (Neri et al, 1995; Wesnes et al, 2003), panax ginseng (Kennedy et al, 2001b; 2007; Sunram-Lea et al, 2004), acetyl L carnitine (Salvioli and Neri M, 1994; Thal et al, 1995), bacopa monniera (Maher et al, 2002; Stough et al, 2008), sage (Tildesley et al, 2003; 2005; Scholey et al, 2008), melissa officinalis (Kennedy et al, 2002; 2003), alpha lipoic acid (Hager et al, 2001), guarana (Kennedy et al, 2004), essential oils & aromas (Moss et al, 2003; 2008), pycnogenol (Ryan et al, 2008) and thiamine (Haskell et al, 2008). Benefits have also been identified with energy drinks (eg Scholey and Kennedy, 2004) and chewing gum (Wilkinson et al, 2002).

The Way Forward in this Field

The level of evidence required in this field should not differ from any other field of clinical science. Therefore randomised, double-blind placebo controlled trials must be employed, and cognitive test systems utilised which are fit-for-purpose for the requirement of detecting enhancements to various aspects of cognitive function. Only properly characterised substances should be tested, and standardised extracts are clearly essential to allow replication in different laboratories. Safety is of crucial concern; only substances which have an established safety profile should be evaluated and safety should be carefully monitored in any clinical trial in this field. One large well-conducted study has just been accepted for publication which satisfies these various requirements. The trial evaluated the effects of Docosahexaenoic acid (DHA) on cognitive function in 485 elderly people who fulfilled the DSM-IV criteria described earlier for AACD (Yurko-Mauroa et al, 2010). Six months of supplementation was found to produce statistically reliable improvements to memory. Though the effect size of the improvement was small (0.19), as with the Wesnes et al (2000) trial, the computerised cognitive assessment system used in the study had a normative database; and using this database the authors were able to identify that the effect reflected a seven-year reduction in normal ageing (3.4 years when compared to placebo), which may well be attractive to the population studied (mean age 70 years). An important aspect of this study was the careful monitoring of safety; the adverse events not being different between the placebo and active treated groups. Besides being conducted to the rigorous standards required in this field and carefully monitoring safety, an important aspect of the study for future research was the presentation of effect sizes as well as an assessment of the potential 'cognitive age-reducing' effect of treatment.

Conclusions

Until worldwide regulatory bodies recognise the cognitive declines in normal ageing as a legitimate target for drug development, individuals who wish to seek to reduce age-related declines in mental efficiency should follow recommended guidelines for optimal levels of physical exercise and diet, as well as partaking in mental exercise; which while not widely demonstrated to help protect against mental decline, is almost certainly not harmful. In addition, the availability of well-standardised nutritional and natural products with established safety profiles which have been convincingly demonstrated to possess cognition-enhancing properties will be attractive to many. Many widely available substances are showing such potential, and developers of such products have the opportunity to structure their research programmes to fulfil the various criteria and standards described here, in order to bring products to the market which can help counteract the cognitive declines which appear to occur in the majority of individuals as they age, without compromising their general wellbeing. ●

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Professor Keith A. Wesnes, BSc PhD FSS CPsychol FBPsS

- Practice Leader, Specialty Clinical Services United BioSource Corporation.
- Visiting Professor, Division of Psychology, Northumbria University, Newcastle, UK.
- Adjunct Professor, Brain Sciences Unit, Swinburne University, Melbourne, Australia.

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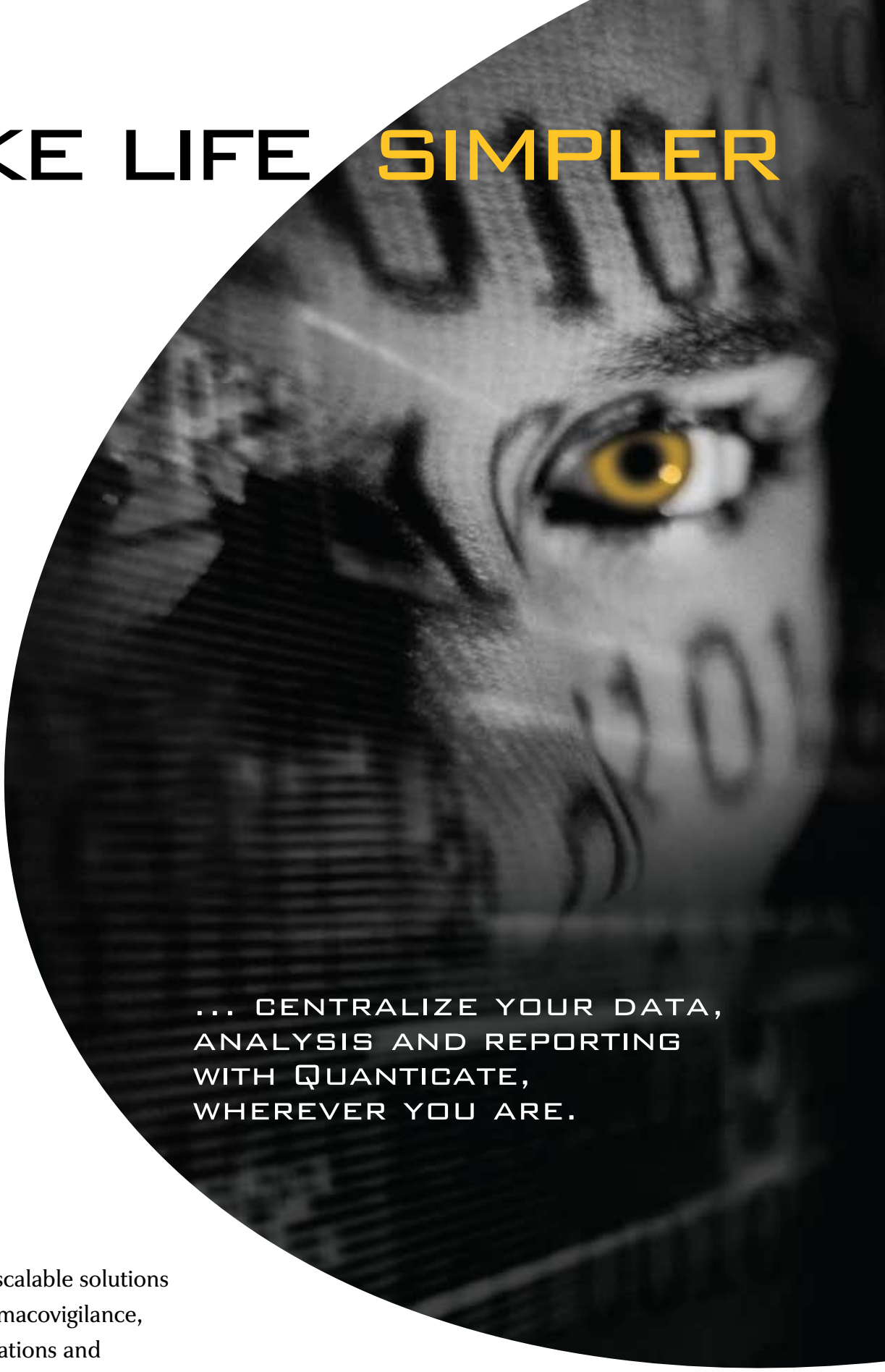

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Shipment of Biological Samples and Clinical Trial Supply in Emerging Markets

Site Selection – Who Thinks about the Effect on Logistics Budget?

We are frequently consulted for new clinical trials about shipping costs from various countries that are expected to be included, many of which are considered to be from emerging markets. What we rarely have in hand during the early stages is an idea of where the sites may be located within those countries, which can make planning ahead and budgeting more problematic.

In the tried and tested markets, given our experience of many thousands of studies, we have a fairly good idea of what breakdown may be expected in primary, secondary and tertiary cities, and whether we have already negotiated fixed rates for the duration of a clinical trial. However, more studies now include sites in India, China and the Asia Pacific region in addition to the expected Eastern European countries (these really are part of our normal profile nowadays). With little information as to the spread of sites this may have a serious effect on transportation budgets as the site list populates.

Other important considerations relating to budget are whether the study will competitively recruit, and the experience the sponsor or CRO has of working in these areas. We know from past experience that some Eastern European sites can recruit rapidly and a key site may be many kilometres from the countries' point of export, raising courier costs considerably by the end of the study.

Other matters affecting shipping costs may be the requirement for rapid turnaround times to ship to the central lab to report key parameters within 48 hours of sampling, collection of samples on demand, or the need to see patients seven days per week and when specialised packaging is required to be provided at the point of collection. In such cases the Logistics department tends to utilise a specialist courier that has the flexibility to meet such requirements.

Temperature Control of Biological Substances and Packaging Solutions

In our industry we frequently refer to different types of shipping temperatures, in particular those that are associated with the strict guidelines of cold chain logistics for Investigational Medicinal Product (IMP). However, a central laboratory faces three main shipping temperatures – ambient, refrigerated and frozen – and often, combinations of these types in a single shipment.

So what is "Ambient" Temperature?

This will depend on where you are geographically located and is generally considered room temperature – for those of us in Europe we would consider this somewhere around 18-25°C. However, in Asia Pacific temperatures are frequently much higher than this for much of the year, and in Russia, Ukraine, Japan and China we see very cold winter temperatures. Samples can be in transit for 24-48 hours, during which time they may be:

- sitting in a collection area in a hospital
- in a courier's van
- awaiting loading onto a plane
- in a cargo hold during a flight.

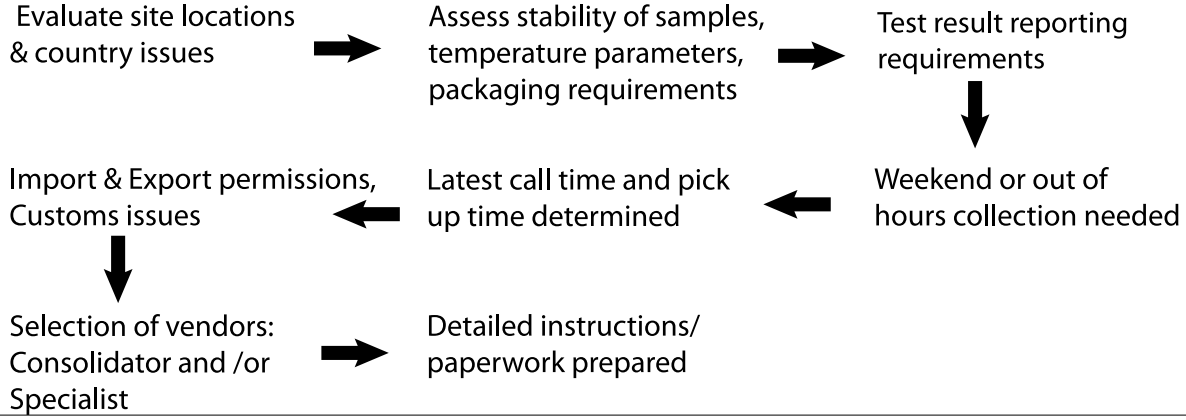
For these reasons ICL recommends additional packaging options in areas that are more commonly subject to extreme heat or cold – parts of the AsiaPac region utilise a thermal ambient shipper and an extreme ambient shipper to protect against cold in Russia, Ukraine and parts of Japan/China.

Refrigerated Shipping

This is usually defined as 2-8°C and is one of the more challenging to maintain, being subject to external temperature considerations.

All of the packaging supplied by ICL is qualified by the manufacturer and is either bought "off the shelf" if it fits our requirement, or may have been commissioned by ICL for a specific

Courier Selection Guidelines



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Protect from Cold - Average Lows (Celsius)

Country	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
POLAND	-3	-3	---	3	7	11	12	12	9	5	---	-1
ROMANIA	-5	-3	---	5	10	14	15	15	11	6	---	-2
RUSSIA	-9	-8	-4	---	6	11	13	12	7	2	-2	-6
SWITZERLAND	-1	-1	1	3	7	11	13	13	10	6	2	0
UKRAINE	-9	-8	-3	2	8	12	13	12	8	2	-2	-5

Protect From Heat - Average Highs (Celsius)

AUSTRALIA	28	28	28	26	23	21	20	21	23	25	27	28
CHINA	7	8	11	18	23	27	31	30	26	22	16	10
HONG KONG	19	19	21	25	28	30	31	31	30	28	24	21
INDIA	20	22	28	35	38	38	33	32	33	32	27	21
INDONESIA	28	29	30	31	31	31	31	31	31	31	31	30
JAPAN	8	9	12	17	22	24	27	30	26	20	16	11
KOREA, S	3	3	9	16	22	26	27	28	25	18	10	8
MALAYSIA	31	32	32	32	32	32	31	31	31	31	31	31
NEW ZEALAND	19	19	18	16	13	11	10	11	12	12	15	17
PHILIPPINES	30	31	32	33	33	32	31	30	31	30	30	30
SINGAPORE	29	31	31	31	31	31	30	30	30	30	30	29
SOUTH AFRICA	25	23	23	20	18	15	16	18	21	22	23	24
TAIWAN	18	18	21	25	27	31	33	32	30	26	23	20
VIETNAM	18	19	22	26	30	32	32	31	31	27	24	21

purpose and external temperature protection profile. One of the challenges with refrigerated packaging is ensuring that it is correctly conditioned ahead of introducing the samples and ensuring that the qualification will match the expected transit time along with contingency plans should the shipment be delayed. Most refrigerated systems use a rigid thermal inner box and an arrangement of frozen and ambient gel packs all within a cardboard outer sleeve. It is very important that the manufacturer's conditioning is followed carefully, and this can be an added burden to the investigator site. Does the site have sufficient storage space to keep the bulky packaging and -20°C freezer space to keep the gel packs? Do they have time to prepare the shipping boxes? What happens if they use other gel packs not meant for the box? Will a courier need to supply pre-conditioned gels and box on same day of shipment? There are solutions to these questions but they can have a significant impact on budget.

Frozen Shipping

This is actually an easier temperature to maintain for considerable time – but will be subject to a number of options that will affect budget, such as required transit time, size of box, number of samples, external temperature, access to dry ice, etc. Dry ice (or frozen carbon dioxide gas) comes in several forms, and we most commonly see pellet form. In the past the shipment and supply of dry ice has been handled by the specialist carriers, but this service is now offered in many countries by most couriers in both central and local supply models. An important consideration in selecting the carrier for certain regions is whether the dry ice can be replenished if the shipment is subject to a delay beyond the qualified time the box has been tested to.

Liquid nitrogen shipping is gaining popularity as it offers some protection for critical samples navigating the variability of international shipping, and is considered a "green solution" from refrigerant used to the recycled packaging service model. The current cost models are high, but will reduce with the economies of scale when services are provided in association with large integrated couriers.

Site Training/Compliance with IATA Guidelines

Training is an essential part of ensuring the safe transportation of Biological Substances, and any person involved in the preparation or transport of such material by air, road or sea is required to be trained to comply with shipping regulations in accordance with the Department of Transport (DOT) and the International Air Transportation Association (IATA). Biological Substances Category B are designated as Class 6.2 Dangerous Goods and Dry Ice is a Class 9 which requires careful handling and may pose a hazard to those handling it during its journey. This subject is a frequently visited topic for all central laboratories, and one which deserves an article in its own right.

What About Import and Export Permits?

The discussion of regulatory issues around importation of clinical trial materials and export of biosamples for the APAC-Asia Pacific region is a very broad topic with a constantly changing regulatory environment that should be addressed on a per country basis. Great care must be taken to ensure these considerations are addressed during protocol design and protocol setup by the laboratory. The plans made by a sponsor before discussion with central lab project management and logistics team may not work due to the regulatory environment of a country selected for participation in a study. We would like to approach the subject by first addressing challenges of clinical trial material supply.

The sponsor's early collaboration between laboratory, CRO or sponsor's local affiliate office is critical to the success of a CTM distribution plan. The emerging markets have had some bad experiences with counterfeit medial devices and quality issues with approved items. There are a few tactics or techniques that can be used to effectively import CT materials to a site, and also many factors and considerations that weigh on the decision as to the selected approach; here are some of the examples:

- The selected countries in the trial and their customs clearance processes

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- Number of sites per country
- Frequency of kit re-supply request by sites
- In-country representation – ability of party to act as importer of record
- Country customs import regimes – formal or informal, sometimes both
- Requirement for import permits for lab collection kit components
- Competitive enrolment – variability in supply distribution to sites
- Expiry date of kit supply materials – three, six, nine months?

Since sites themselves usually do not have the knowledge or authority to execute a Power of Attorney (POA) for customs clearance, or know their own VAT or GST tax numbers, it is important to minimise the activities required of the site for the import process. Depending on the individual country's import regulations, there a few ways to limit the need for site participation in the import process:

Direct to Site, Site as Importer – where there is no import permit required, supplier of the CTM sends materials directly to site, indicating site address as importer on a single airbill and proforma invoice. Customs clearance is handled by courier or subcontracted partner arranged by courier.

Direct to Site – use of Importer of Record (IOR) – supplier sends CTM addressed to site with commercial invoices noting site as ultimate destination, and IOR indicated on invoices for customs clearance purposes. Using the importer of record avoids any need for site to have a customs profile on record.

Direct to Hub – CRO or sponsor contracts a local company to physically accept shipment at their hub warehouse or airport facility and hold in inventory for supply requests directly from sites. Supply shipments are then sent as domestic movements via local courier services. There are a number of risks and benefits with this approach, and shipper's distribution responsibility ends at shipment turnover. This is a popular method used to address complex import requirements and lengthy turnaround times for imports. This is often seen as a 'safety net' option.

Direct to Site – "virtual hub" – we often use a special contract arrangement made by ICON Central Laboratories and the carrier, with authorisations obtained from a qualified importer to use them to clear shipments, with the courier as a virtual hub. Shipments are redistributed directly from the courier operations centre with the orders individually packed by site number. The courier simply uses one of two methods: (1) the "domestic" airbill labels are preprinted by C-lab, and the courier applies them to packages for domestic distribution; (2) the courier manifests shipments on a local shipping system using document labels on packages to create domestic airbills. There are significant cost benefits compared to a brick and mortar hub approach. Shipments travel, and priced as "heavy" freight move to the destination facility. Local distribution to site costs are calculated and passed back to shipper. There are no setup costs, "in and out" costs for materials, per shipment handling fees, or inventory reporting fees. Materials do not sit, potentially expiring before use.

Early Contact with Importer

The importer of clinical trial materials and exporter of biological substances should be given the latest information and customs clearance documentation to ensure the items are described in the best way to indicate compliance with government regulations and protect against automatic triggers for "hold for inspection" by customs officials. Some of these triggers can be based on total weight of shipment, weight of each box in shipment, or total value of shipment in relation to the weight.

As mentioned earlier, it is critical to have discussions as early as possible to avoid study startup delays for FPFV (first patient first visit) due to CTM availability in country. A best practice of ICON Central Laboratories has been to obtain a regulatory contact for each country. When the contact is obtained, introductions via email are sent to identify the individuals or groups that will exchange information for the purpose of obtaining import permits, approving shipments to be sent to country and obtaining proper names to be used as importers by the shipper.

Import Process

Participating countries need to be reviewed to confirm if they need import permits. If yes, is an import permit needed for each shipment? If a permit is not required for each shipment, does the country require renewal of permit? What is the duration of import approval period? Is it for length of study or set period requiring renewal? Is there a quantity limit for the import of kits? Who is responsible for keeping track of kit imports and destruction of unused kits? These are important items that need to be considered when setting up a process.

For some APAC countries, such as Taiwan and South Korea, supporting manufacturer's information such as address of company and country may be required to obtain an import permit. Often, the manufacturers' certificates of compliance in accordance with US 21 CFR 820 and 21 CFR 903 are requested for international shipments. Pictures of materials to be imported may be also requested for permit application along with item numbers, model numbers and harmonised tariff system codes.

Once the import permits are confirmed as being in place, the initial supply and recurring cycle of re-supply are set in motion. Upon receipt of orders from sites, the supplier will create the commercial invoices related to the order and send for approval. Typically the identified responsible party will confirm the description and quantities of materials to be sent, to conform with the import permits obtained. Often the carrier tracking numbers are supplied to be used to begin the import clearance process or monitor the import process of materials to sites.

Export of Samples

In the APAC region, currently only China and Taiwan require export permits for the shipment of UN3373 shipments. The People's Republic of China has recently announced changes to the application process and regulatory body that will accept and approve the export of biological materials. In P.R. China, two ministries, the Ministry of Health (MOH) and Ministry of Science & Technology (MOST) are in discussion to combine the administration on permit application for human origin specimens with the Human Genetic Resources Administration of China (HGRAC) approval; the leading group in MOH is inclined to transfer the administrative power to HGRAC under MOST, and the committee of specialists will continue discussion in the coming weeks.

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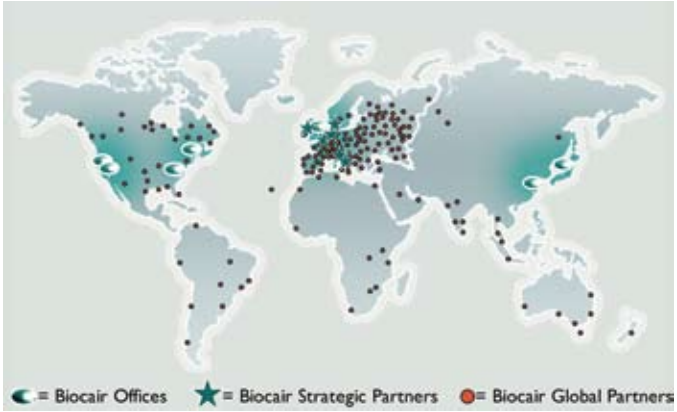

Contact Details:

USA, Boston
Tel: +1 (617) 623 0544

San Francisco
Tel: +1 (650) 685 5511

San Diego
Tel: +1 (858) 549 9800
Email: sales@biocair.com

UK, Cambridge
Tel: +44 (1223) 245 223
Email: sales@biocair.co.uk

China, Shanghai
Tel: +86 (21) 6160 1550
Email: sales@biocair.cn

Japan, Osaka
Tel: +81 (0) 6-6644 6664
Email: sales@biocair.jp

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The disadvantage of the function transfer is the time of application. Under MOH's jurisdiction, it usually takes less than one month (10-30 working days) to obtain the permit; the specialist appraisal is once a month - but for HGRAC, the appraisal turnaround time will be much longer, as it currently takes place once every three months (on a quarterly basis). Moreover, if it is for human genetic resources, the applicant for HGRAC approval must be a Chinese collaborator; for example, the investigator will take care of the document endorsement but not pharma companies, which will give the sponsors or CROs a challenge.

We understand that HGRAC is planning to draft a new regulation to cover all human genetic samples exported out from China, especially for human serum & plasma, and they are trying to shorten the application time-line for human serum and plasma, but it might take time before it is implemented.

The Importance of Contingency Plans!!!!

Whatever and wherever you need to move Biological Substances, it is essential to know that your laboratory partner has robust contingency plans in place with their suppliers to maintain the integrity of patients' samples - and what an essential plan this proved to be in recent months, particularly in Europe!

However, even the best business contingency plan may not have covered a total shutdown of much of Europe's airspace for such a prolonged period of time. Our vendors were able to switch to alternative road services (with some added extras that were put into place at very short notice). We offer our sincere thanks to all those involved in the efforts taken to move the samples that were in transit during this time and to our staff that worked round the clock to analyse them!

We suggest your contingency plans consider the value of having export permits which allow for more than one lab destination listed for sample shipments in the event of natural disaster, civil unrest or other unforeseen events. •

Brian Torpey Director, Logistics, ICON Central Laboratories, New York. Brian has over 20 years operations management experience in international express logistics while with UPS and Airborne Express air and ground operations. Brian is experienced in global customs brokerage operations and currently responsible for the global distribution of Clinical trial materials for ICON Central Laboratories.
Email: brian.torpey@iconplc.com

Caroline Brooks BSc, is Associate Director, Logistics, ICON Central Labora-tories, Dublin. Caroline has worked within the pharmaceutical industry for over 20 years. With a BSc in Medical Laboratory Sciences she started work in a teaching hospital in the UK before joining one of the early pioneers for Central Clinical Trial laboratories in London. In 2001 she moved into the specialist courier business to apply her experience in support of the supply chain for Clinical Trial and in 2008 returned to the central laboratory arena at ICON in Dublin to ensure that sponsor, investigator and laboratory get the best service possible from their courier partners.
Email: caroline.brooks@iconplc.com

Russia & Eastern Europe Subsection

Many changes have taken place in the EU's political and regulatory landscape which has had an impact on clinical research in Central & Eastern Europe (CEE). Over the last ten years, clinical research in CEE has been and is continuing to be one of the fastest -growing regions in Europe. This is due to the Centralised Healthcare system with many large policlinics and specialised hospitals together with a good selection of quality investigational sites from many teaching hospitals, medical schools and universities. In 2010, Russia's population is 142million whilst Ukraine has 45million inhabitants, followed by Poland with 38million and Czech Republic with 10.4million. Poland, Hungary and Czech Republic have the largest number of clinical registrations studies (over 1000) followed by Russia. According to a report by PMR entitled "Clinical trials in Poland 2010. Development forecasts for 2010-2012", if barriers to market growth, including unclear legislation and difficult trial registration procedures at the Central Register of Clinical Trials (the CEBK), were removed, the clinical trials market could develop even more rapidly.

A Press release by PMR in 2010 discusses the progress of The Clinical Trials Act. The Clinical Trials Act has been in preparation for years; the objective of the act is the regulation of clinical trials through the clarification of existing regulations and the addition of new areas which have not previously been subject to legal regulation. The assumptions underlying the bill were published in December 2009, whereas the bill is expected to be ready in the first half of 2010. Among other things, the Clinical Trials Act will clarify and amend regulations applicable to the proceedings of ethics committees.

Dr. Patricia Lobo, MSc, PhD, Managing Director & Senior Consultant for Life Science Business Solutions (LSBS)
Email: plobo@lifesciencebusinesssolutions.com

Clinical Trials in Russia. 1st Quarter 2010

The Federal Service on Surveillance in Healthcare and Social Development of the Russian Federation (alias RosZdravNadzor, RZN) approved 134 new clinical trials of all types including local and bioequivalence studies during the first quarter of 2010 demonstrating an 18% increase over the corresponding period of last year.

The main contribution into the total number of studies is made by multinational multi-center clinical trials, the number of them also increased by 15% over Q1 2009 and stood at 83 new studies in Q1 2010. The number of the local clinical trials conducted in Russia by domestic and foreign sponsors is also up from 27 to 36 clinical trials demonstrating a notable 33% increase over the same point in 2009. Clinical trials in Russia in Q1 2010 were sponsored by companies from 20 countries. The maximum number of trials (44) were initiated by Russian sponsors, American sponsors with 30 studies took the runner-up place, they are followed by German sponsors with 10 trials, eight new studies were instigated by the UK and Swiss manufacturers, and the top six is concluded by French sponsors with seven new studies in Q1 2010.

Eleven new Phase I clinical trials were launched in the first quarter of 2010; seven trials up over the corresponding quarter of last year. The number of the Phase II trials increased by 27%, from 26 trials in the first quarter of 2009 to 33 studies in the first quarter of 2010. The number of Phase III trials demonstrated a 7% increase over last year number, up from 59 to 63 studies. The number of patients which are planned to be enrolled in the Phase II-IV trials launched in the first quarter of 2010 stood at 13,016 patients, demonstrating a 25% increase over the last year number.

The Swiss Novartis sponsoring seven new studies is on the top of the heap in the first quarter of 2010. GlaxoSmithKline with six new trials in Q1 2010 took the runner-up place. It is followed by Pfizer also sponsoring six new studies, but with less number of patients, and French Servier with four new studies. The top five is concluded by Merck & Co. having three new studies in Q1 2010. The Russian pharmaceutical company OAO Sti-Med-Sorb sponsoring four new clinical trials enrolling 290 patients in five sites, ranked number one among domestic pharmaceutical manufacturers by the number of new studies in the first quarter 2010. OOO Geropharm with three new trials and 480 subjects in 11 sites took the runner-up place. It is followed by ZAO Infamed, ZAO Biocad and AKO Sintez with two studies each differing only in the number of patients and sites.

Sixty nine per cent of the new studies in Q1 2010 were conducted in the six leading therapeutic areas. The maximum number of trials (28) were initiated in Oncology; 12 clinical trials in Respiratory diseases; nine new studies in Psychiatry; seven new studies in Cardiovascular, Infectious and Musculoskeletal diseases were initiated in Q1 2010.

Anna Ravdel, Director of Business Development at Synergy Research Group (SynRG).
Email: ravdel@synrg-pharm.com

Clinical Trials in Russia?

Synergy Research Group!

For more information, please contact Igor Stefanov (istefano@synrg-pharm.com), or visit www.synrg-pharm.com

Optimising Time and Money in Clinical Trials – Russian, Ukrainian and Eastern European Perspective

A decade ago many US-based and Western pharmaceutical companies were sceptical and slow to realise Russia's great possibilities for clinical trials, and especially for fast patient enrolment. Now in 2010, most pharmaceutical and biotech companies have become much more savvy and experienced in conducting clinical trials in this part of the world. As a result most in our industry are well versed in the strengths that Russia and Ukraine offer: a combined population of 200 million, a centralised and vertical healthcare system, millions of patients who consider trials as an opportunity to receive good healthcare (many of whom are drug-naïve), and hundreds of well educated and motivated physicians/investigators who desire to participate in the clinical trials process. Together, these factors give rise to great geographies for high quality, fast-enrolling clinical trials. Most of the large pharmaceutical companies as well as a good number of mid-sized and small biotechs have discovered these advantages, as evidenced by the increased number of companies conducting trials in this region.

No	Sponsor	Number of Studies	Number of Sites
1	GlaxoSmithKline	58	315
2	Bristol-Myers Squibb	36	250
3	Pfizer	36	113
4	Sanofi Aventis	36	73
5	Eli Lilly	34	83
6	AstraZeneca	26	110
7	Hoffman-La Roche	21	188
8	J&J	20	213
9	Novartis	16	42
10	Boehringer Ingelheim	15	100
11	UCB	10	32
12	Astellas	9	43
13	Bayer	7	7
14	Novo Nordisk	9	10
15	Organon	9	55
16	Solvay	9	79
17	EORTC	7	8
18	Merck	7	26
19	Altana	6	6
20	Biogen Idec	6	40
	Other	142	914
	Total	519	2,707

Table 1: Top 20 Sponsors Conducting Clinical Trials in Russia in 2000 – April 2007. Source: Synergy Research Group – Clinical Trials in Russia, Orange Paper

Therefore, it would be a waste of the readers' valuable time to rehash these points. Instead, we would like to focus on what we think are the next set of key questions, i.e.:

What results are biopharmaceutical companies achieving by conducting trials in these geographies?

Are they saving valuable time and, therefore, money?

Are regulatory approvals being obtained using data from trials conducted in Russia, Ukraine and other parts of Eastern Europe?

Without regulatory approval and product availability in the marketplace, fast enrolment and high quality brings little benefit to the patients and limited success to companies and their executives and investors. In this article we attempt to answer these questions.

Are Companies Saving Time and Money by Conducting Studies in Russia, Ukraine and Eastern Europe?

While Russia, Ukraine and Eastern Europe are not the least expensive regions in which to conduct clinical trials, there are many attributes that lead to greater cost efficiency than in North America or Western Europe. Two of the more obvious contributors are the lower hourly rates of Russian and Eastern European CROs, and lower investigator/hospital grants than in the West.

However, this difference is becoming less significant as the number of CROs multiplies and the cost to retain and recruit qualified individuals to perform clinical trials increases accordingly. In addition, the growing number of trials and competition for qualified investigators, especially in the large cities such as Moscow, St. Petersburg, Novosibirsk and Kiev, is causing the gap between Eastern and Western fees to diminish.

To address these trends, we are expanding the investigator base into the regions of Russia and Ukraine. Most regional hospitals have qualified physicians who are enthusiastic to trial opportunities while having access to the necessary equipment. As the cost of living in the regions is lower than in the large cities, the reduced salaries that regional clinical trial professionals command enable local CROs to keep their cost structures intact while still providing cost-competitive pricing.

The less obvious but significantly more important cost advantage of Russia, Ukraine and Eastern Europe relates to the ability to enroll patients up to 20 times faster than in the West. The timely conclusion of patient enrolment averts operational costs associated with delays and ultimately, allows products to be brought to market in a more timely manner, thus enabling the revenue stream from product sales to commence much earlier.

Cost of Operational Delays

In a survey of 49 executives and chief risk officers of pharmaceutical, biotech and device companies, as conducted by McKinsey and Lehman Brothers, 85-95 % of those polled cited slow patient recruitment as the main cause of delay in clinical trials. Utilising the average cost per patient in Phase II and Phase III trials as obtained from "Cutting Edge Information" and combining such data with generally accepted assumptions regarding the average number of patients and duration of studies, we calculated that the operational cost of a delay could be from $160,833 to $1,083,333 per month. The data is summarised in Table 2. Decreasing the enrolment period by up to 20 times (and thus the total study duration) by conducting studies in Russia, Ukraine and Eastern Europe can lead to significant cost savings.

	Phase II	Phase III
Average cost per patient	$19,300	$26,000
Average number of patients	200	2,000
Average length of studies	24 months	48 months
Average trial cost per month	$160,833	$1,083,333

Table 2: Average Monthly Operational Cost of Clinical Trials.

Loss of Future Product Sales

Bristol Myers Squibb President stated in 2001 that "Every second of delay in a clinical trial costs Bristol-Meyers Squibb $17." This provocative statement caught our attention and we decided to try and substantiate it. First we looked at the annual and daily sales of blockbuster drugs. As seen in Table 3, the average daily sales of a blockbuster product is $15.6 million US dollars.

We then applied the following simple maths:

Average daily sales for a blockbuster = $15.6 million USD
86,400 seconds in a day
$15.6 million divided by 86,400 seconds = $181 per second

Therefore, the lost opportunity cost from the delay of bringing a blockbuster drug to market is $181 per each second of delay.

Noting that not all drugs are blockbusters, we then applied the same methodology to niche medications.

Drug & Company	"2005 Global Sales in billions (USD)"	"Average daily sales in millions (USD)"
Liptitor (Pfizer)	12.9	35.3
Plavix (BMS)	5.9	16.2
Nexium (Astra Zeneca)	5.7	15.6
Advair (GSK)	5.6	15.3
Zocor (Merck)	5.3	14.5
Norvasc (Pfizer)	5.0	13.7
Zyprexa (Lilly)	4.7	12.9
Risperadal (J&J)	4.0	10.9
Prevacid (TAP)	4.0	10.9
Effexor (Wyeth)	3.8	10.4
Total	56.9	155.7
Average	5.7	15.6

Table 3 Blockbuster Drug Sales Source: IMS MIDAS Quantum

The McKinsey & Company Quarterly reported that "Delays can cost pharma companies at least $800,000 a day in lost sales for a niche medication, such as [Sanofi-Aventis'] Amaryl, an oral anti-diabetic treatment."

Using Amaryl as an example, the cost of delay for niche medications could be calculated as follows:

Average daily sales for Amaryl = $800,000 US
86,400 seconds in a day
$800,000 million divided by 86,400 seconds = $9.25 per second

The cost of delay for getting a niche medication to market is $9.25/ per second. Considering the fact that BMS markets both blockbusters and niche medications, the figure presented by the President of BMS is very plausible.

Every possible effort should be made to complete studies faster. Conducting clinical trials in Russia, Ukraine and Eastern Europe, where enrolment rates are up to 20 times faster than in the West, provides this opportunity. Are Companies able to Obtain FDA and EMEA Approvals using Pivotal Data coming from Trials Conducted in Russia, Ukraine and Other Parts of Eastern Europe?

The answer is "yes". To date, we know of products that were approved where part of the pivotal data came from Russia, such as: Abraxane and Ixempra for breast cancer, Glustin for diabetes, Nuvigil for sleep disorders, Invega for schizophrenia, Vesicare for overactive bladder, Tesigna for myeloid leukemia, etc. The list is growing. ClinStar has managed several trials in which the data has been utilised to gain regulatory approvals. One example was our participation in a neurology study that was being conducted at 43 sites spread across North America, South America, Western Europe, and Asia Pacific. We were requested to add 12 sites in Russia and Lithuania. ClinStar caused these 12 sites to enroll 60.6 % of the patients in the entire trial and the product was approved by EMEA and Health Canada; it is currently pending approval at the FDA. Russia, Ukraine and Eastern Europe represent productive geographies with fast-enrolling clinical trials. These trials, with the patients and pivotal data coming from Russia, Ukraine and Eastern Europe, enable biopharmaceutical companies to bring their products to market in a cost-effective way while optimising time and money during the pharmaceutical product development process. ●

David Passov, ClinStar's President and CEO, was born in Estonia when it was part of the Soviet Union. He attended Tartu University Medical School in Estonia prior to moving to the US in 1993. He received a degree in biology from Boston College and following short basic science research tenure at Massachusetts General Hospital's neuroscience department entered the biopharmaceutical industry in 1996. Since that time, he has held positions in clinical operations, project management, market research, business development and commercial operations at various small and large US-based CROs. Mr. Passov also received an MBA from the Executive MBA Program at the Northeastern University (Boston, MA) in 2002. He joined ClinStar in 2005. Mr. Passov is a native Russian speaker and spends about 75 percent of his time in ClinStar's offices in Russia and Ukraine.
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Comprehensive Feasibility Assessments in Eastern Europe – Luxury or Necessity?

Longer R&D timelines and the escalating costs of clinical trials, particularly in highly developed countries, has driven many pharmaceutical and biotechnology companies to examine the potential benefits of enrolling subjects in Eastern European countries. However, for many sponsors, operating in Eastern Europe can be a daunting prospect. In this article, we will examine how sponsors can be best positioned to take advantage of the benefits of emerging clinical trial locations.

Conducting trials in emerging markets such as Eastern Europe offers the appealing prospect of substantive gains, including:

- Rapid recruitment of clinical trial investigators and subjects
- Significant cost benefits
- Conducive hospital infrastructure and healthcare systems
- Enhanced clinical site effectiveness
- Health needs of the population under study

However, to tap into these rewards requires a detailed understanding of a number of additional key areas which have the potential to negate some or all of the perceived upside and generate frustration amongst those responsible for delivering a trial. Importantly, this knowledge needs to be acquired prior to taking the decision to include Eastern European countries within the country selection for a particular trial. So what should an informed sponsor consider as fundamental to this knowledge base? Points to include are:

- The transparency and efficiency of regulatory systems
- Assimilation of individual national regulations and guidelines
- Harmonisation and standardisation of regulatory requirements
- Expansion of CROs
- Concerns over clinical trial transparency
- Availability of demographic and epidemiological data
- Ethical challenges and ethical oversight
- Language translations
- Clinical trial logistics
- Import licenses and applications
- Customs regulations
- Storage, handling and distribution

The Importance of Feasibility

It is well recognised that during the planning phase the development of a study-specific knowledge base through feasibility assessments is critical to the ultimate success of any clinical trial. This process should be designed such that the gathered information is all-encompassing and robust, thereby ensuring that an appropriate decision can be made about any country and at any particular site as to both the feasibility and achievability of meeting the study goals.

Nevertheless, feasibility assessments are still, in general, poorly performed even in well-developed trial territories. The reasons for this are probably multi-factorial, but include amongst others:

an overall perception that

- All parts of the process will ultimately come together
- Someone somewhere within the delivery team will know or have access to specific parts of the puzzle
- Historical trial and site data can reliably be transformed into present day knowledge
- Regional familiarity will reduce the risk of trial 'failure' in terms of timelines and budgets

and a reliance on a legacy model that assumes

- Running a feasibility assessment must mean any particular trial is feasible
- A feasible study must be an achievable study
- The quality of any feasibility data acquired will be the same regardless of the stage of development of the protocol
- Accurate feasibility can be generated within a matter of days

The outcome of poor feasibility frequently dictates a failure to achieve successful delivery of specific clinical trials on time and within budget.

The Critical Importance of Feasibility in Emerging Markets

Based on the above it can be reasonably postulated that high quality feasibility assessments are of even greater significance to trial success in, what for many will be, the less familiar emerging market territories of Eastern Europe. The often-voiced market drivers are clear:

- Large eligible treatment-naïve population who exhibit high retention rates
- Large pool of dedicated, well trained and motivated investigators
- Centralised healthcare systems and well-developed referral systems
- Enhanced clinical site effectiveness (patients per site) in the emerging countries
- Fewer ineffective sites in the emerging countries

but the perceived potential barriers are equally as important:

- Poor hospital infrastructure with inadequate medical equipment
- Cultural differences and issues
- Possible delays importing and distributing the study drug
- Lack of clinical trial experience amongst hospital staff and hospital services
- Lack of hospital resources, particularly dedicated and experienced clinical trial teams
- Healthcare system variations

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- Regulation and legislation issues
  - Ministry of Health requirements and approvals
  - Territorial self-government administration approvals
  - Other regulatory authorities

So how can the prospect of these barriers be reduced to the extent that the upside of clinical trial delivery in Eastern Europe can be maximised? The answer is perhaps threefold:

- Planning
- Process
- Detail

Planning

Start early. Merely considering involvement of Eastern European countries in a clinical trial should trigger, at a minimum, an exploratory feasibility assessment, with more detailed assessments following on with countries and sites that meet the study requirements. Historically, the 'start feasibility early' concept has been poorly utilised with many sponsors allowing CROs to perform these tasks at a later stage as part of a trial bidding process, and as a site identification exercise, rather than a true feasibility assessment. The risks for the sponsor are again high with this approach and, if pushed, it would probably be fair to say that most sponsors have had mixed results. CROs of course have a vested interest in making sure any feasibility assessment meets both their and the sponsor's requirements, but that should be tempered by then having to deliver the study - historically not always a sequitur.

Process

Standardise. High quality feasibility assessments need a clearly-defined process in order to acquire comprehensive data and to assimilate and analyse the outputs into meaningful decision-grade information. A list of investigator site names or locations does not constitute feasibility. Furthermore, flexible processes allow a feasibility assessment for an individual clinical trial to be revisited subsequent to protocol changes or sponsor requirements without reinventing the wheel based on 'first round' information.

Detail

What goes in determines what comes out. The importance of accurate up-to-date data cannot be stressed enough with regard to developing a study-specific knowledge base. Investigator sites change, standard of care changes, regulatory processes change. The business of clinical trial delivery is in constant flux. So reliance on historical data is a high risk approach.

From an investigator site perspective, the quality of the acquired data is only as good as the knowledge of the respondent allows. So it becomes imperative to ask the right question of the right person at the right time. Achieving this is not a straightforward task. For example, asking a busy Investigator in the middle of a clinic as to the current ethics process, timelines and dates is unlikely to generate the desired response. Systems that allow individuals at investigator sites to contribute to specific responses and build their own investigator site profiles go a long way to achieving this goal, and in addition can:

- Avoid repetitive questioning
- Facilitate comprehensive site data collection
- Allow data to be collected at a time suitable for the sites
- Allow confirmation of site data at the time of a potential new study
- Allow the investigator to focus on the study-specific issues that ultimately drive feasibility and achievability at that site

However, the investigator site profile is only part of the puzzle. The study-specific part of the feasibility assessment needs to be derived from all the available relevant information from the sponsor, and tailored according to the stage of development. This means that exploratory feasibility is just that and can rely on a smaller package of data, whereas detailed confirmatory feasibility requires trial planning to have progressed much further down the track. As such, in the latter case the data should ideally include a protocol that is final enough to allow any one investigator to determine their interest in the research questions, the depth of their involvement in the study, their access to the target subject population and their realistic subject recruitment projections.

Consideration should be given to language issues here. For the information to be meaningful, ensuring the investigator site personnel have a clear understanding of the proposed trial is critical. As such, sponsors should not be reticent in adopting an early translation policy for critical trial information rather than utilising ad hoc local translations.

How to Make Feasibility in Emerging Markets Work

Understand what you need to know and how to obtain the information. For many clinical trials, contracting out feasibility assessments to those with extensive experience is the most expeditious way to acquire the information. Providers with global coverage offer the benefits of standardising both the information provided to investigator sites and the data outputs from the process, thereby allowing seamless integration of Eastern European countries into the clinical trial delivery environment.

Summary

Feasibility is changing in response to market dynamics, and nowhere is this more important than in the clinical trial emerging markets. Unknown or poorly understood processes at best lead inevitably to frustration, timeline delays and increased costs, and at worst to ineligible clinical trial data.

Undoubtedly, the potential benefits of including Eastern European investigator sites into clinical trials encourages the taking of some element of risk, but this can be substantially mitigated by conducting high-quality feasibility assessments prior to selecting countries and sites. Such assessments may be contracted out or performed in-house by sponsors. Either way it is important to recognise that the costs so incurred need to be considered as an investment in clinical trial success, and in many cases would be significantly less than the costs associated with, for example, delays in site selection or subject recruitment.

Dr. Guy Patrick, MD PhD – Director and Chief Medical Officer: Dr. Patrick is a co-founder of Centrical Global Limited, a specialist global clinical trial feasibility company providing services to a broad range of Pharmaceutical and Biotechnology companies. Having trained as a Consultant Nephrologist and Immunologist, he formerly worked for Omnicare Clinical Research prior to co-founding Premier Research Group plc, a leading full service CRO.

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The Costs Involved in Conducting Clinical Trials

Although the cost of conducting clinical trials varies enormously, largely due to differences in the scope of particular trials, clinical trials are always expensive exercises. Total trial costs generally break down into the following categories:

- Investigator site costs (personnel, equipment, procedures, etc) 35-40 % of cost
- Trial management and monitoring 25-30 %
- Cost of drug supplies 10-20 %
- Logistics (packaging, shipping, handling) 10-20 %

With 60-70 % of the total costs being due to a combination of investigator site costs and trial management costs, it makes sense to look at these two aspects more closely.

The fees charged by investigators and medical institutions generally reflect the levels of costs, including physicians' salaries, in different countries. These costs vary widely from country to country; site costs in the US can be up to three times those in Eastern Europe, Latin America or Asia. The law of supply and demand also plays a role here; good sites are always in high demand and there are often situations where different trials are "competing" to include patients from the same patient pool. In this situation, which trials will be favoured may depend not only on factors such as the degree of academic interest in a given study, the rigidity of the inclusion and exclusion criteria and the complexity of the procedures required, but also the financial remuneration for the investigators or institution. This is why the fees paid to the investigators and the sites must be competitive, in order to ensure achievement of recruitment goals and timely study completion. In some indications and some countries where the clinical research market has not been as fully developed, it may be possible to find sites where there is less competition for patients. But while this may mean that the investigator fees are lower, these sites usually require some additional investment by the trial sponsor in the training of site personnel and more intensive management during the study.

Site "saturation" and site staff workload are very important factors, as overloaded sites will accept participation in new clinical trials only if the financial reward is attractive. This is one of the reasons why we are observing a rapid escalation in site costs in those countries which are becoming popular for clinical trials, eg in Central and Eastern Europe, Latin America, India and China. The level of the site fee may also depend on whether the study is run by a CRO or local sponsor subsidiary, or directly by the sponsor company's headquarters. It appears that if the sponsor has well-established local operations, runs a lot of trials itself, and knows the local market well, the fees negotiated with sites are usually lower than where a CRO is responsible for negotiations with the site. This difference may be because the sponsoring company and the CRO have different priorities when it comes to site negotiations; CROs wish to motivate site performance with attractive fees, while sponsors may be more keen to keep costs under control. The level of the site fee may also depend on the profile of the sponsor within a given country, the marketing priorities of the sponsor, and the need for the sponsor to gain access to new sites.

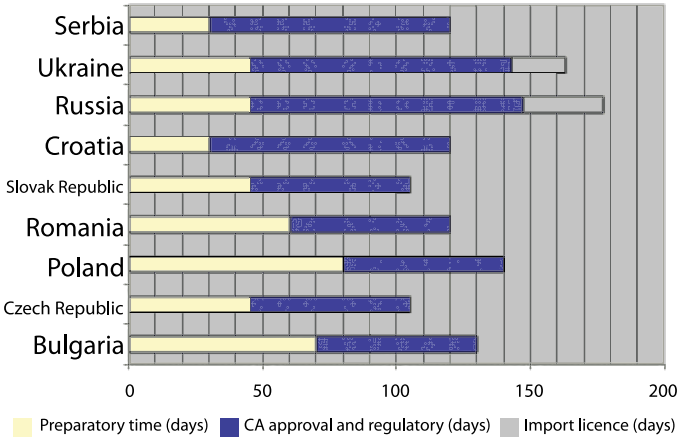
Within each country a thorough knowledge of the marketplace for clinical trials, medical salaries, and the costs of procedures and materials in public and private institutions is essential. In emerging markets it also has to be kept in mind that many healthcare systems have suffered from under-investment for years and the facilities in some countries need to be improved to bring them up to international standards. Fees paid may need to include upgrades to facilities and equipment in order to ensure the quality of the project.

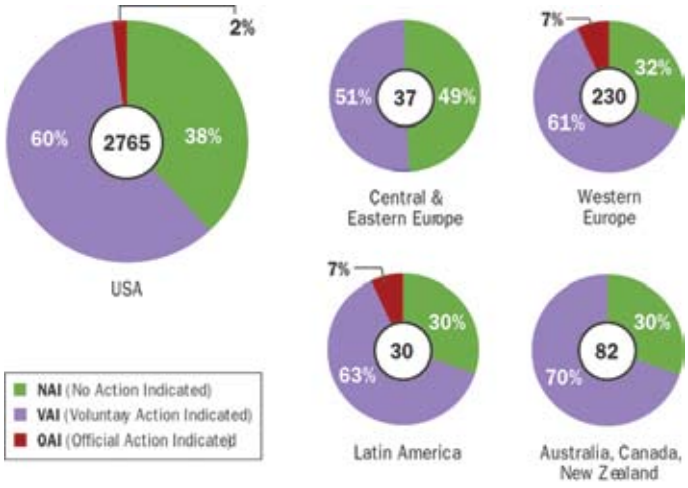
Besides investigator site costs, the second major component of trial cost is for trial management and monitoring. The costs of these activities are very much related to the quality of personnel resources allocated to the studies, their experience and their local expertise in regulatory matters. There is some evidence that when a project is outsourced to a CRO, there is greater control over the total cost, and milestones are more likely to be achieved on time.

One of the factors to be considered when using a CRO to manage a study is how experienced the CRO is in dealing with the procedures required in each of the participating countries. They must have local regulatory resources and expertise, good relationships with the chosen investigator sites, and be flexible and adaptable with respect to executing contracts with sites and carrying out the local logistics. This is why project management is such a key function and, depending on the CRO, may make up 20-35 % of the total CRO's budget. It should be noted that the above costs are "direct" costs; there are also many "indirect" costs, most of which are time-related, i.e. those that influence the overall duration of a study. These indirect costs can be managed by choosing the right sites and countries for conducting a clinical trial. Obviously one would prefer to go to sites in countries which have high numbers of suitable patients, and where patients are motivated to give consent to participate in a given trial, eg by having access to procedures and treatment which would otherwise not be available to them.

Regulatory timelines in potential countries also need to be considered. Although there is a high degree of standardisation between countries in the documentation required to obtain authorisation to conduct clinical trials, regulatory timelines vary considerably. In general there are two separate processes involved in obtaining approval for clinical trials: approval by government regulatory authorities, and approval by competent ethics review

Start up and regulatory timelines in Central and Eastern Europe





bodies (depending on the country, these may be national, regional or local institutions). Different countries have different requirements regarding whether submissions to these two processes can be done in parallel or have to be sequential, ie approval from a government regulatory body is required before submission to ethics review bodies, or vice versa. My own company has considerable experience in the different countries of Central and Eastern Europe; the following table illustrates our own experience with regulatory timelines.

In addition to financial and time considerations, another critical success factor is obviously quality. When data obtained are "clean", ie error-free and not requiring clarification of omissions and inconsistencies, less time and effort are required before databases can be locked for subsequent analysis. As an indicator of quality, a recent study compared the outcomes of FDA inspections conducted outside the USA with those conducted in the USA. In this comparison, Central and Eastern Europe (CEE) compared very favourably with other regions, and with the USA itself, and may partly explain why this region has become so popular for clinical trials in the last 10 years. (Asia was not included in this comparison due to the low number of inspections performed during this period.)

As I stated at the outset, clinical trials are always expensive and complex undertakings. The economics of drug development demand a highly developed discipline in clinical project management, particularly so when trials are conducted outside of the traditional and relatively similar regions of North America and Western Europe. The attraction of conducting trials in Central and Eastern Europe, Latin America and Asia is that these countries can offer access to large numbers of patients at significantly lower cost, so that by carefully selecting regions, countries and sites for trials and managing them to ensure maximum data quality, these cost savings may be achieved without sacrificing quality and regulatory acceptability. ●

Malgorzata Szerszeniewska MD, has many years of experience in managing clinical trials in Poland and other countries in Central and Eastern Europe. After completing her MD in Warsaw, she joined an international pharmaceutical company, then in 1996 she started the Polish operations of Covance. She was Covance's Head of the Central and Eastern European region before becoming President of AbCRO, a regional CRO based in Bulgaria. In 2009 she co-founded EastHORN, where she serves as its Chief Executive Officer.
Email: malgorzata.szerszeniewska@easthorn.eu

Drug Information Association (DIA)-22nd Euro Meeting in Monaco 2010

Monaco was the destination of this year's DIA 22nd Euro Meeting at its state-of-the-art Grimaldi Forum. IPI and JCS had the pleasure of attending this splendid Meeting. The DIA Annual Euro Meeting is the largest event of its kind in Europe. Over 3,000 professionals from biopharmaceutical industry, contract service organizations, academic research centers, regulatory agencies, health ministries, patient organisations and trade associations were at Monaco from 8-10th March 2010.

The meeting was flooded with sessions, networking and booth talks. Some selected highlights were: Pharmaceutical IT-Systems Architecture, Semantic-Service Orientated Architecture, Risk-Based Quality Management, Validation of PDF Rendering results vs. Source Documents and Regional Network Rheine-Main-Neckar and sessions on Clinical Trials. "As I've had the opportunity to travel, one of the things I've learned is that probably one of the greatest assets that DIA has is its training programs." Paul Pomerantz said-Worldwide Executive Director DIA.

On the theme of training and sessions, JCS particularly found tutorials 8 and 12 of interest. Tutorial 8 focused on Adaptive Designs for Confirmatory Clinical Trials with Heinz Schmidli the Senior Expert Statistical Methodologist of Novartis Pharma AG, Switzerland. This was an excellent introduction to the theory and practice of adaptive designs for pivotal clinical trials. Adaptive designs allow for mid-course design modifications such as the adjustment of sample size, the dropping of treatment arms or the selection of a subpopulation. Reviewed and discussed were the statistical methodologies that allow such adaptations without compromising the overall type I error rate.

Jürgen Kübler (tutorial 12) the Global Head-Statistical Safety Sciences at Novartis Pharma AG, Switzerland and Joachim Vollmar, Executive Consultant of International Clinical Development Consultants, USA homed in on a combination of theory, guidelines, practical considerations and real-life solutions for those working in the clinical development environment and was aimed at providing a basic understanding of the underlying methodology and the current guidelines on safety data. Aspects regarding the planning of clinical trials as well as the problems and pitfalls during the analysis of safety data were portrayed.

In today's world of austerity, Mats Ericson, Regulatory Policy Director of Amgen, France explored the highly relevant topic of the possibility of simplification of EU Clinical Trials Framework by exploring the ways to reduce administrative burdens and to streamline the regulatory supervision of clinical trials in the EU, shorter- and longer term. A recent initiative is the so called voluntary harmonization procedure ('VHP'). In the field of Exploratory Clinical Trials in the EU, David Laurie a Regulatory Policy Expert, DRA Management at Novartis Pharma AG, Switzerland explored Regulatory guidance such as ICH M3, recently consolidated exploratory clinical trials as an approach to perform early compound selection based on data in humans. This session explored and reviewed recent regulatory changes and experiences, industry decision-making regarding exploratory clinical trials, and GMP aspects of investigational medicinal products used in such early clinical studies.

Focus on EU continued with contributions from David Jones, Expert Pharmacotoxicologist at MHRA-UK; Brian Ledwith, Global Compound & Program Management Lead, Merck-UK; Walter Janssens, Senior Assessor Pre-Clinical Department Research & Development, Federal Agency for Medicines and Health Products, Belgium to the Implementation of GMP in Exploratory Trials Ailsa Searles, Qualified Team Leader of Pfizer, and UK. At the Media Roundtable Paul Pomerantz, the New Worldwide Executive Director Shared DIA's Vision for 2010 and beyond. "DIA is the global forum for knowledge exchange that fosters innovation to raise the level of health and well-being worldwide." The new DIA vision statement

Pomerantz also said: "As a transformative organization, we're moving from focus purely on pharmaceuticals to all types of regulated medical products…" and "…..It also means that we're looking at the entire ecosystem of medical products that deal with not only drug development and design but also the regulatory process and its use in the patient care environment." Pomerantz made clear his intention to make DIA a global organization in a broad sense. "Whereas we served a constituency that was perhaps considered heavily pharma, as the industry changes, it will be expanded to those who are in medical devices, health technology assessment, informatics, biotechnology, diagnostics, patient groups, etc. The idea is that our forums will become larger and more diverse

as we move forward. We'll both expand globally and deepen on a regional basis."

The Grimaldi Forum was a very impressive waterfront venue allowing for considerable networking. Monaco was a superb. JCS and IPI are very much looking forward to attending next year's DIA Conference in Geneva.

Testimonials:

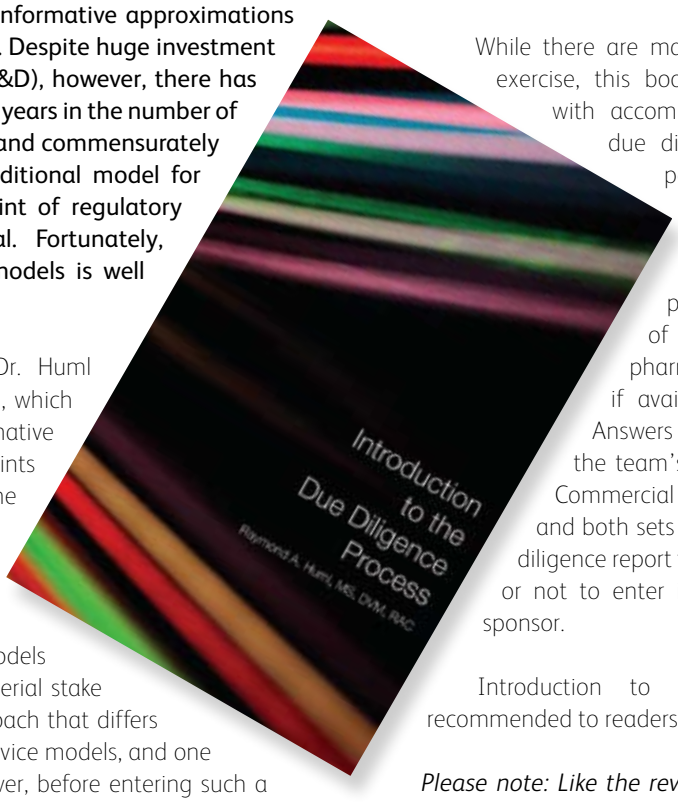
"Once again the DIA Annual Euro Meeting was an ideal opportunity for us to meet some of our existing clients and also meet some new prospect clients.....this is without doubt the best event of its kind, attracting around 3,000 professionals from over 50 countries working in the biopharmaceutical industry" – Michael Ellis - Business Development Manager UK and Italy - CLS Communication Ltd

"We found the interest and feedback from investigators extremely valuable towards helping us to identify new opportunities." Mike Bradshaw M.I.L.T Senior Vice President OCASA Health Division

"As usual Euro DIA lived up to expectations in bringing together the great and the good from the entire spectrum of clinical research stakeholders throughout Europe. ERT received an unprecedented amount of sponsor and partner interest due to the European launch of its Centralized Cardiac Safety 2.0 initiative (www.ert.com/ecg) and it is apparent that the green shoots of recovery are evident now throughout the sector. ERT very much looks forward to its participation at Euro DIA 2011 in Vienna and to continue to support its European clients and partners with unrivalled solutions and services." Patrick Hughes, Head of Marketing, ERT.

Introduction to the Due Diligence Process by Raymond A. Huml

New drug development is a lengthy, expensive, and complex endeavour. While precise quantification of 'lengthy' and 'expensive' is difficult, respective values of 10-15 years and US$1.3 billion are realistic and informative approximations to bring one new drug to market. Despite huge investment in research and development (R&D), however, there has been a downward trend in recent years in the number of new drugs reaching the market, and commensurately increasing concern that the traditional model for bringing a new drug to the point of regulatory approval is no longer optimal. Fortunately, the search for more effective models is well underway.



In his very readable book, Dr. Huml describes new partnering solutions, which he defines as "new forms of imaginative collaboration that avoid constraints of conventional approaches." Some such solutions can be provided by contract research organisations (CROs) working in partnership with pharmaceutical and biotechnology companies in models in which "both parties have a material stake in the product's success," an approach that differs considerably from earlier fee-for-service models, and one that can be very successful. However, before entering such a partnership, the CRO will want to conduct a due diligence process.

The path to bringing a new drug to market has many obstacles, including potential regulatory, scientific, preclinical, clinical, manufacturing, legal, financial, and commercial hurdles. To minimise the chance of failure in any of these domains, a team of experts will conduct a due diligence exercise. As the author notes, due diligence includes "a thorough investigation of all available data — both proprietary and nonproprietary — by a team of experts with the intention of predicting future events, such as the probability of success and a forecast of sales, in order to equip a deal team to manage risk and execute a financial transaction."

While there are many aspects to a full due diligence exercise, this book focuses on R&D due diligence, with accompanying discussion of commercial due diligence. When considering a new partnering development opportunity, members of the R&D team will address various aspects of the investigational drug, including its proposed indication, mechanism of action, safety (toxicology, safety pharmacology, and clinical safety data if available at that point), and efficacy. Answers from all these considerations enable the team's assessment of the product profile. Commercial due diligence can then be executed, and both sets of results combined into a final due diligence report that informs the decision on whether or not to enter into a partnership with the drug's sponsor.

Introduction to the Due Diligence Process is recommended to readers, and receives the JCS Library Award.

Please note: Like the reviewer, Dr. Huml is an employee of Quintiles.

Regulatory Affairs Professionals Society
2010
Soft cover, with compact disc
126 pages
US $99.95
ISBN: 0-9787006-4-3

J. Rick Turner, PhD, Editor-in-Chief, joined the journal's Editorial Board this January. He is Senior Scientific Director, Cardiac Safety Services at Quintiles, and also an accomplished author and editor who has a real passion for books. We are pleased to announce that Rick has agreed to become Editor-in-Chief of a new addition to our journal, the JCS Book Corner. He will be reviewing books of interest to our readership, and giving JCS Library Awards to outstanding books that should be in your company's library, or perhaps even in your personal collection. On occasion, he will be inviting other Editors to review books too.

Rick's first book was written while he was actively involved in research in the field of Cardiovascular Behavioral Medicine. Entitled Cardiovascular Reactivity and Stress: Patterns of Physiological Response (1994, New York: Plenum Press) it was the first student textbook examining the putative role of psychological and behavioral stress in the development of high blood pressure, and potentially other cardiovascular sequelae. The journal Psychophysiology commented that "Cardiovascular Reactivity and Stress is an extremely readable and well organized text… As an introduction to the field, Turner's book is a superb resource." Rick edited four other books in the field of Behavioral Medicine before moving into the pharmaceutical industry in 1996.

Since being in this industry, Rick has published three books discussing various issues within new drug development. The first, New Drug Development (2007, Hoboken, NJ: John Wiley & Sons) was a general overview of this topic. The Journal of Applied Statistics commented that "The book gives a refreshing run through of the drug discovery and development process and it is probably the book you need to have to learn about this fascinating field." An updated, expanded, and less technical second edition will be published later this year by Springer Science (New York). His other books, both co-authored with Todd Durham, are Introduction to Statistics in Pharmaceutical Trials (2008, London: Pharmaceutical Press) and Integrated Cardiac Safety: Assessment Methodologies for Noncardiac Drugs in Discovery, Development, and Postmarketing Surveillance (2009, Hoboken, NJ: John Wiley & Sons).

We are delighted that Rick is bringing his publishing experience and his love of books to the journal, and we particularly look forward to featuring books written by our readers. If you would like to submit your book to the JCS Book Corner for review, please ask your publisher to send a copy to: **Pharma Publications, Building K Unit 104, Tower Bridge Business Complex, Tower Point, London, SE16 4DG**

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