



ASEAN All-Stars

While lower costs may have attracted pharma companies to south-east Asia, it is the ability to recruit large numbers of patients that is keeping them there. Garry Muddyman of Conversis explains how choosing the right language providers is key to maximising success

The clinical trial landscape has changed dramatically over the past decade. Whereas at the turn of the century, almost all clinical trial research was carried out in the US and Western Europe, US-based drug sponsors indicate that up to 50 per cent of studies are now conducted outside of the US and expect that figure to increase to 65 per cent within three years (1). In 1990, clinical trials were conducted in about 28 countries worldwide. In September 2009, the FDA was regulating 78,276 trials in 172 countries, and the European Medicines Agency (EMA) expects the trend to conduct more clinical trials in developing nations to increase in years to come.

There are a number of reasons for this shift. Lower costs, access to large numbers of treatment-naïve patients, the potential for fast patient recruitment and the opportunity to expand their presence in emerging markets are among the top reasons pharmaceutical companies are now conducting trials in developing nations. South-east Asia is an increasingly popular destination because it offers all of these benefits.

SOUTH-EAST ASIA AS A DESTINATION FOR CLINICAL TRIALS

The Association of south-east Asian Nations (ASEAN) is a growing regional force within Asia. It is made up of 10 nations including Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Burma, the Philippines, Singapore, Thailand and Vietnam. These 10 countries have a land mass of 4.5 million km², a population of 580 million, and a combined gross domestic product of \$1.5 trillion, with a growth rate of 4.4 per cent in 2008 (2).

This represents a huge potential market for pharmaceutical companies, particularly as healthcare markets open and the prevalence of Western lifestyle diseases such as Type 2 diabetes increases. Indeed, according to IMS Health figures, the Asia Pacific region represents almost 11 per cent of the global pharmaceuticals market and is continuing to grow, year on year.

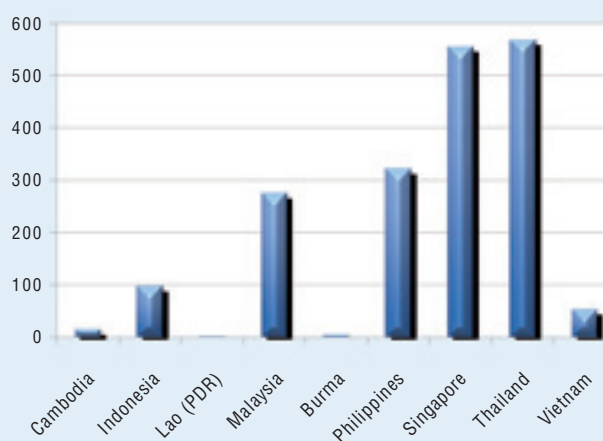
Up to now, it has been the five original members states of ASEAN – that is

Indonesia, Malaysia, the Philippines, Singapore and Thailand – that have received the most investment in terms of clinical trial research.

In September 2009, the FDA was regulating 96 trials in Indonesia, 273 in Malaysia, 322 in the Philippines, 553 in Singapore and 564 in Thailand (see Figure 1) (3).

There are a number of reasons why these particular countries are appealing to drug sponsors. Reduced costs is often cited as one of the primary reasons, and it is true that clinical trials can be conducted at a fraction of the cost of those in the West, owing to lower human resource costs, lower investigator fees and lower costs of patient recruitment. But there is one factor encouraging drug sponsors to conduct their research in south-east Asia that overrides all the others, and that is the ability to recruit large numbers of patients very quickly.

Figure 1: Number of FDA-regulated clinical trials in ASEAN countries (as of 1st September 2009)



The name of the game in today's pharmaceutical market is to speed up time to market. Any time taken off the drug development phase is highly valuable: the shorter the time to market, the longer the effective patent life, the greater the potential earnings of the drug.

Patient recruitment and retention has become a major bottleneck in clinical studies in the traditional research countries. Patient recruitment is the main reason for study delays and studies show that between 60 and 70 per cent of all multicentre randomised controlled trials in the UK fail to meet their recruitment target (4). In the US, CenterWatch puts this figure at 86 per cent. A McKinsey report noted that taking a single month off a trial by improving recruitment could generate an additional \$40 million in sales, so you can see why the potential for fast recruitment is such an attractive option for drug sponsors (5).

A largely treatment-naïve population, combined with the increasing number of patients with Western lifestyle diseases such as heart disease and Type 2 diabetes and the high incidence of other diseases such as hepatitis, provide a huge potential resource in south-east Asia for drug sponsors.

A sympathetic medical infrastructure also aids patient recruitment and retention. The fairly centralised health system allows for easier patient recruitment, and the long-term relationship that tends to exist between physician and patient, keeps retention rates high and allows for the all-important long term follow up.

Physicians have shown a strong desire to participate as investigators in recent years, especially as a means to improve their professional competence. Most companies entering the region have required all new investigators to undertake training in the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP). These are generally considered the universal standards for conducting clinical trials in the US, Western Europe and Japan.

It is because of investment of this type that there now exists in south-east Asia a strong clinical trial infrastructure with high standards to match that of the West. Many centres have been established over the past five years, most attached to public hospitals or academic institutions, and GCP and other ICH guidelines are now well-understood in the region.

Holding trials in south-east Asia also provides drug sponsors with the opportunity to collect data on epidemiological differences across ethnicities and demographics. This data is of interest both to the healthcare payers, who are looking for ways to raise healthcare standards across multicultural populations, and to the pharmaceutical companies who are interested in the development of more 'personalised' medicine and treatment for niche diseases.

SINGAPORE'S SUCCESS

Recognising the attractiveness of their nations to the global pharmaceutical industry, many south-east Asian governments

have identified the life sciences as an area of economic growth and have gone to great lengths to encourage investment. Through its Biomedical Sciences Initiative, the Singapore Government, for example, has made a considerable effort over the past 10 years to attract investment from multinational pharmaceutical companies – and the efforts have largely met with success.

Among Singapore's initiatives was the building of the Biopolis: an integrated, purpose-built research complex of public and private research laboratories. Complemented by shared scientific facilities and other services, the biomedical research complex is designed to stimulate interaction and collaboration between industry and public research laboratories. The Government is also involved in a number of public-private partnerships, which make the prospect of investment in Singapore all the more attractive.

Recent announcements of public-private partnerships (PPPs) include GlaxoSmithKline Biologicals committing \$1.3 million in vaccine and process development with Singapore's Bioprocessing Technology Institute; Lilly Singapore Centre for Drug Discovery teaming up with Singapore's National Neuroscience Institute; and the Singapore Institute for Clinical Sciences to advance drug discovery using adult brain tumour stem cells. AstraZeneca has also announced its collaboration with the National Cancer Centre Singapore and the National University Hospital in preclinical and clinical development activities of anti-cancer compounds to build up AstraZeneca's drug development capabilities in Asia.

Singapore now has more than 500 clinical studies taking place on its shores, and an increasing number of them are early phase trials. The Malaysian government also offers a number of research grants and initiatives to encourage life sciences investment. But it is the cooperation of ASEAN nations to coordinate regulatory procedures that is bringing the real benefits to the region and to drug sponsors.

THE REGULATORY ENVIRONMENT IN SOUTH-EAST ASIA

ASEAN's stated purpose is to accelerate economic growth, social progress and cultural development in the region. For a number of years the Association's Consultative Committee for Standards & Quality has been working towards harmonisation of pharmaceutical regulations. In July 2009, agreement was finally reached. The stated aims of the harmonisation process are to create a transparent regulatory process; to standardise regulation requirements; and to remove the need for duplicate studies to meet various regulation requirements, thereby allowing drug companies more time and resources for the research and development of new drugs.

As soon as 2010, drug companies should be able to go through one set of regulatory requirements for all ASEAN countries so long as they are compliant with the ASEAN Common Technical Dossier (ACTD). So far, only five per cent of the drug industry in the Philippines is compliant so

it remains to be seen how quickly the harmonisation will take to become truly beneficial (6). It should, however, make the prospect of multicentre trials across south-east Asia more attractive, more cost-effective and more straightforward.

LANGUAGE AND CULTURAL CONSIDERATIONS

Language and culture will play a major role in any clinical trial undertaken in south-east Asia, and should not be taken lightly. Inaccurate or insensitive translations could not only lead to delays, but to ultimate trial failure.

While these nations are close in geographic terms, it would be a mistake to assume an inherent cultural affinity. Indeed, different languages are spoken, and depending on trial protocol (and therefore target patient population), many trial documents will need to be translated into more than one language per country.

In Malaysia, for example, it is not uncommon for patient and investigator materials to be translated into Malay, simplified Chinese and Tamil. In the Philippines, documentation would normally be translated into Tagalog and Cebuano, both considered 'rare' or 'specialised' languages. In the large Indonesian archipelago, however, it is usually sufficient to translate into Bahasa Indonesia and, similarly, Thai alone is sufficient for Thailand.

It goes without saying that particular care must be taken in the translation of clinical study documents for patients: tone, terminology and accuracy are all of paramount importance. But it is often more than mere translation that is required.

Patient recruitment posters and leaflets will usually require an element of localisation if they are to be as effective as possible. The localisation of patient recruitment materials may involve a simple process such as changing photography to feature local people, or it could entail the more involved process of adapting words and phrases to account for local understanding of Western concepts, or changing colours and symbols, which have very different meanings across the region.

This process involves a careful mix of local knowledge and medical expertise. An agency with proven experience in the region, which has a network of local medical translators, should be used to help with this process.

Apart from recruitment, there are perhaps two other areas that will require

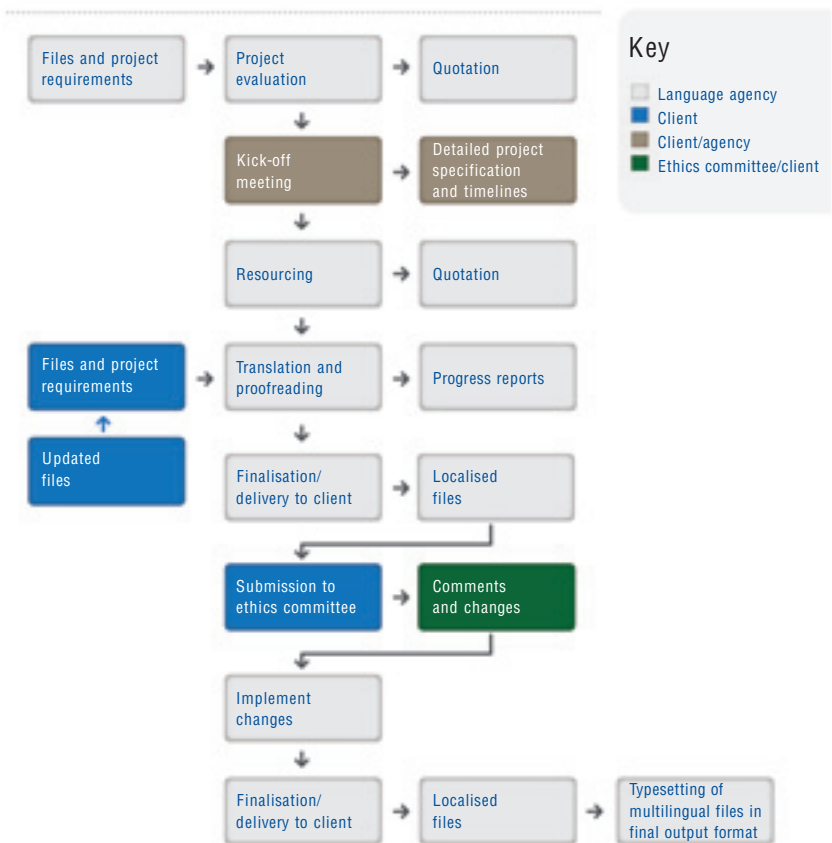
careful translation and localisation: patient and investigator information materials, including informed consent forms, and patient reported outcomes.

As a general rule of thumb, most patient information materials are written for a young target reading age, often about 12 years of age. This is to account for varying literacy levels, as well as for the fact that many patients may still use another language or dialect as their first language at home. It is important that the tone of these materials is open and honest, not overly scientific and not patronising in any way. The purpose is to give the patient information about what the trial will involve – including the risks – and what is expected of them. Translations must be careful not to provide false hope. Translations must also take into account local understanding of Western concepts such as the placebo. In some patient populations, there may be no existing knowledge of such a concept, and great care must be used to communicate its meaning and context.

For all these reasons, most documents will require forward and back translations with approvals through a variety of sources. A typical process may include the following steps (see Figure 2 for a typical workflow process for language services):

- ◆ English documents supplied to translation agency
- ◆ Documents translated into applicable languages

Figure 2: Localisation process flow for international clinical trials



- ◆ Documents back translated into English
- ◆ Forward and back translations provided to client's in-country reviewers
- ◆ Country reviewers provide amends to agency and are accepted/rejected as necessary in consultation with specialist translators
- ◆ Country reviewers send final copies to ethics committees
- ◆ Ethics committee approval received or amends made
- ◆ Documents supplied to translation agency for typesetting

Informed consent will form a vital part of the localisation process. Different cultures will have different rules about who makes decisions within the family and community. While these social norms must be respected in gaining informed consent, they can never replace the consent of the individual. The process of gaining informed consent therefore can be particularly onerous on the part of the investigator.

Varying levels of literacy will also affect the traditional Western method of collecting informed consent through a printed form with signature. The World Medical Association's Declaration of Helsinki is the leading guidance on ethical issues in conducting clinical trials in developing countries and drug sponsors should make sure that, in addition to following the ICH Guideline of Good Clinical Practice, investigators are *au fait* with the ethical principles involved in collecting informed consent, as well as the regulatory requirement to properly document it.

Patient reported outcomes (PROs) are also a significant factor to consider in international clinical trials, and how they are translated will depend largely on how they are collected. Cultural issues must obviously be taken into consideration. In many regions in south-east Asia, telephone interviews simply are not an option. Allowing patients to fill in questionnaires at home where they may be influenced by family members or figures of authority is also a consideration to make when deciding on the method of collection. Generally, a member of site staff conducting patient interviews provides consistency

About the author



Gary Muddyman is the Managing Director and CEO of Conversis, a leading provider of globalisation, internationalisation, localisation and translation services, specialising in the life sciences sector. Gary started Conversis back in 2003 with the intention of advancing the

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and quality of data, and there are now many well-trained staff in the region.

The emergence of tools such as EuroQol EQ-5D questionnaire does make collecting PROs easier. EQ-5D is a standardised instrument that measures health outcomes and it is currently available in 83 languages.

However, it is not just a matter of document translation and localisation. If a drug sponsor wants to have a long-term presence in this region, they will need to establish meaningful and culturally appropriate relationships with research institutions, investigators and regulatory authorities. This requires an understanding of local culture and business etiquette. Most global pharmaceutical companies and many of the biggest clinical research organisations (CROs) have established a regional headquarters and the development of these relationships is well underway.

CONCLUSION

South-east Asia is well established as a centre for conducting high-quality clinical trials, with ICH Guidelines for GCP now standard practice. The large patient pool, the potential for fast patient recruitment and an increasing number of well-trained investigators makes it an attractive region for investment for global pharmaceutical companies.

Co-operation between regional governments under the auspices of ASEAN has led to the agreement of a standard set of regulatory and approval guidelines, which will make conducting multicentre trials across the region a cost-effective and straightforward process.

There remain, however, vast and important cultural and language differences in the south-east Asian region. These must be understood and respected. The quality of translations in clinical trials affects ethical issues such as informed consent and can affect the quality of data as well as ultimate trial outcome. A language partner with experience in the region should be taken on to help drug sponsors get this right.

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