

# Managing Pharmaceutical Globalisation: A Work in Progress

Like a high-speed train, globalisation in the pharmaceutical industry is accelerating steadily, driven by factors too numerous to name – growing healthcare reform and awareness, slowing growth in traditional markets, the imperative to reduce drug development time and costs, and the opportunity to leverage aging populations and emerging markets.

While the advantages of going global are obvious, globalisation creates new challenges that the industry will need to address moving forward. Consider for a moment the complexities associated with conducting clinical trials in China, manufacturing in Ireland and Singapore, and marketing medicines and vaccines in countries as distinct and far-flung as Argentina, Poland and Japan.

Here we will briefly examine the pharmaceutical industry's considerable progress in the ongoing journey called globalisation, as well as the issues that are cropping up along the way. One thing is certain: resolving them will require the same energy and diligence that a train engineer applies to negotiating an unfamiliar curve in the tracks. (1)

## Harmonisation Remains Critical

Aside from the twin drivers of economics and demographics, perhaps the single most important factor enabling globalisation is the substantial progress to date in the harmonisation of regulatory strategies.

Since its 1990 formation by regulatory authorities and research-based industry representatives of Europe, Japan and the United States, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - ICH for short - has improved the way drugs and vaccines are developed and registered by eliminating redundancy. Driving the need to rationalise and harmonise regulations were concerns that are even more relevant today than they were then: rising healthcare costs, escalating R&D expenses, and the pressure to make new treatments for cancer, HIV, heart disease and other serious diseases available to patients in need with a minimum of delay.

Nearly two decades later, pharmaceutical companies can do what was not possible

then - demonstrate the quality, safety and efficacy of a new drug or vaccine using a single set of clinical studies, provide these data to regulatory agencies in a common format and, importantly, do so electronically. Since a hard copy of the typical new drug or biologics application is composed of thousands of pages, electronic filing is efficient, cost-effective and not least of all, green.

Widespread adoption of harmonisation guidelines has gone a long way to easing regulatory requirements for research-based pharmaceutical companies working to develop and register new products. Today, industry and governments in both ICH and non-ICH countries use state-of-the-art ICH guidelines to address technical issues during the product development process.

Meanwhile, harmonisation activities are continuing. In recognition of the industry's laser-like focus on emerging markets, ICH has established regional harmonisation initiatives representing Asia Pacific, Southeast Asia, South American and South Africa. These steps, which broaden ICH's global cooperation activities beyond its core geographic constituencies, acknowledge the critical role these regions play in the future of the pharmaceutical industry. (2)

## Economics Drive Continued Outsourcing

Even before the recent economic downturn, the pharmaceutical industry was steadily increasing its reliance on outsourcing non-core services such as packaging, labelling, analytical testing and logistics as a means of driving down costs. Now more than ever, with companies under intense pressure to shed fixed assets like packaging facilities, they are turning to strategic outsourcing to fill global operating needs.

While cost is the factor driving outsourcing, sponsors are increasingly recognising the need to weigh skills, experience and track record - as well as cost - in identifying and selecting outsourcing providers. A highly experienced provider who has teamed up with multiple sponsors on successful global projects can offer more than just cost savings, for example. The ability to engage best practices, enhance processes, access regulatory expertise and tap into deep knowledge of target markets

can reduce time and waste as well.

Similarly, having a provider board earlier, when, for example, a global trial is in the planning stages rather than when the pressure to ship product to clinical sites is building, can make a major difference. Providers say their most strategic sponsors bring them aboard in the earliest stages of planning a trial, when the protocol concept and list of target countries are in development, enabling the supplier to begin mapping out deployment strategies months before trial materials are scheduled for packaging and shipping. Suppliers are urging sponsors to regard them as an integrated support system, rather than the provider of discrete functions.

While economic pressures will remain the primary driver, savvy sponsors realise that strategic outsourcing can deliver the added bonus of higher-quality global services at lower cost. (3) (4)

## Supply Chain Issues Predicted to Rise

It stands to reason that the increase in the number of clinical trials migrating to sites in Asia, Africa, the Middle East, Eastern Europe and South America would be accompanied by a host of new issues from a supply chain perspective. ClinicalTrials.gov, the registry of clinical trials taking place in the United States and around the world, recently included more than 72,000 trials taking place in 166 countries.

Thanks to globalisation, the number, size and complexity of clinical trials are expected to rise dramatically by 2010, forcing organisations to confront new challenges in managing the clinical supply chain and completing trials efficiently – this according to a recent benchmarking survey of more than 100 pharmaceutical and biotechnology executives.

Those surveyed reported that only 13 per cent of clinical trial materials shipments arrived on time and even then, one in 10 were incomplete. This suggests that there is a great deal of room for improvement, applying an additional layer of pressure on providers and sponsors.

Sponsors, many of which appear to regard the supply chain as somewhat of an afterthought, may finally have to readjust their thinking. As the number and complexity of global trials grow, lack of

proper supply chain management sharply raises the odds that trials could derail at significant cost to sponsors already facing economic pressures. (5) (6)

### Growth in Biologic Trials Raises Logistical Stakes

Pharmaceutical companies seeking cost savings and rapid patient recruitment are turning to emerging markets that include China, India and Russia, among the top-ranked locations in the world for offshore clinical trials.

The increase in the number of clinical trials migrating to cities like Shanghai, Mumbai and Moscow has been accompanied by a host of new supply chain challenges – from navigating a web of evolving government regulations for drug importation, to ensuring Good Clinical Practice (GCP) at trial sites, and navigating complicated logistical issues in countries plagued by limited infrastructure and experience.

The increased complexity of trials taking place in these and other emerging markets is driven in large part by double-digit growth in the number of studies for biologics, including vaccines and monoclonal antibodies, that require controlled temperature conditions during shipping and storage. Such growth reflects the efforts of sponsors to contain higher

development costs for biologics, which exceed those of the average small-molecule drug by a whopping \$400 million.

From a logistics perspective, the increase in trials of biologics means the stakes couldn't be higher, since loss of temperature control requires replacement of costly product. First and foremost, complying with Good Distribution Practice (GDP) during the movement of product is mandatory for ensuring that material integrity and efficacy are uncompromised. Unfortunately, it's not always enough.

Supply chain managers responsible for transporting an increasing number of biologics for clinical trials are also seeking better ways to monitor and maintain the temperature of materials in transit. One solution under evaluation has been the use of radio frequency identification (RFID) transmitters to continuously monitor temperature-sensitive product.

However, early votes are in and despite offering some value, RFID is no magic bullet. While it can alert supply chain managers earlier about the need to re-ship product upon failure, it has no mechanism for preventing failure and, like mobile phones, must be switched off while in transit by plane. The use of global positioning system (GPS) technology is now being explored. At least for the time being, however - technological innovation notwithstanding

- proper packaging, shipping and storage of biologics continue to be the best ways of raising the odds of safe passage.

So, too, is ensuring that product doesn't sit for extended periods in customs, where the risks of temperature excursion threaten the viability of product. That's why supply chain managers arm themselves with a thorough knowledge of the policies and regulations governing import and use of study drugs in trial markets.

Such knowledge can help to prevent prolonged customs delays in countries like China, where jurisdictional disputes, such as a refusal by regional authorities to recognise drug import licenses issued by national authorities, are all too common. Since country policies and regulations are known to evolve and change without notice, especially in emerging markets, remaining current on the rule book is a top priority.

Another key strategy is the use of a premium courier company with a local presence for assistance in managing the often time-consuming customs clearance. Ground handling on arrival is a highly vulnerable point in the clinical supply chain, especially with respect to temperature-sensitive materials. The use of performance metrics in selecting the right courier companies can go a long way to ensuring reliable, on-time delivery of product.

The use of a centralised, regional distribution centre to receive trial materials improves distribution and logistics efficiencies, while limiting the times when trial drug must pass through customs. Coordination of customs transit locally is also a prerequisite to successful supply chain management.

The distribution centre will receive, book and inventory trial drug using standard operating procedures (SOPs) and a single information technology (IT) system to ensure transparency and prevent inventory issues over the course of a trial. Inventory control with respect to biologics is particularly critical, because shelf life is not definitively known in the early testing stages, and product could fall out of specification in the course of a trial.

The job of the supply chain manager doesn't end once trial materials arrive at individual clinical sites. The supply chain manager must work closely with each site to ensure that storage locations for temperature-controlled drugs are appropriate, controlled and secure, and that the staff understands these special requirements.

That's when an understanding of the language comes in handy, along with good relationships and the ability to read between the lines. In many countries - China, India and Japan among them - a high level of cultural courtesy makes it difficult for



people to say no. The ability to interpret what is actually being communicated is essential, saving time, money and face for all concerned. (7) (8) (9)

### Shared Mission Drives Effective Global Teams

The globalisation of the pharmaceutical industry is taking place at every level, including that of the workforce. Multinational programmes have grown to include non-traditional markets, and establishing a strong global team takes time, just like any relationship. The hurdles are particularly high, however, when the team is spread across continents and time zones.

The most important step in establishing a global team and culture is that of creating a shared sense of mission and goals. For supply chain managers, it is instilling in teams an understanding that patients are waiting around the world. This uniting concept translates across borders, regions, countries, languages and cultures.

Having a common mission is the first step, but companies also need to provide time and opportunities for global team members to meet, know each other and interact face-to-face whenever feasible. In these cost-constrained times, technology can help fill the gaps, but personal meetings are preferred, especially in countries like Brazil and China, where knowing and liking someone can result in smoother business interactions.

Finally, leveraging common information sources such as portals can allow team members to gather information expressed the same way, in the same format – keeping the global team, however widely dispersed, on the proverbial same page. (1)

### Costs at Risk in Some Markets

As the number of clinical trials in emerging markets continues to climb, the cost to import trial drugs, supplies and equipment to some countries is creeping up as well.

In a few emerging markets, customs officials are inflating the valuation of study drugs as a means of generating revenue. In a recent example, a shipment of study drugs valued at \$80,000 six months ago was revalued at \$750,000, driving up import costs and leaving the sponsor with the choice of paying the higher duty charges or dropping the trial site in mid-study. The sponsor paid.

Cost pressures are also being felt in the area of supplies and equipment, which are typically purchased and shipped from a central location. In high-duty countries, where costs to import these items exceed those of purchasing them locally, the strategy is endangered.

The practice of reusing costly equipment such as EEG and ECG machines may also

be ending, as customs officials in a growing number of countries routinely value all trial equipment as new for duty purposes. As a result, equipment may only be used for one study, and some large clinical sites are beginning to amass collections of leftovers. One site in India, for example, has five leftover EEG machines that were provided by five study sponsors.

The motivation to purchase supplies and equipment locally is also the result of the requirement to re-qualify imported equipment in countries such as China and India, which have different electrical standards. The need to re-qualify a piece of equipment, including items like electronic glucose monitors, sometimes boils down to a single wire of an unapproved colour.

### Scientific and Ethical Issues Prompt Debate

While the globalisation of clinical trials offers multiple benefits for pharmaceutical companies and for society, a February article in the *New England Journal of Medicine* suggested that scientific and ethical concerns are mounting.

International standards and corporate and academic oversight must be improved to ensure that research goals are achieved and societal needs are met, say the authors, all of them researchers at Duke University School of Medicine.

They maintain that quality of care, treatment choices, and hospital and clinic infrastructure vary widely between countries, and raise questions about qualifications of individual investigators and review boards, the commitment of local regulatory authorities and the ability of patients to fully understand the implications of testing.

While they acknowledge that standards vary widely among countries, particularly in emerging markets, trial sponsors and outsourcing suppliers contend that manufacturing, packaging and conduct of clinical trials meet a single, consistent global standard, regardless of location.

These scientific and ethical concerns will no doubt continue to be hotly debated, especially as clinical trials grow in number and complexity across the world. The future of the pharmaceutical industry is predicated on addressing these issues, say the Duke researchers. Meanwhile, the train that is pharmaceutical globalisation continues to accelerate. (10) (11)

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