Globalising clinical development in Japan

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Abstract

Most global pharmaceutical companies, no matter where they are headquartered, are struggling to effectively integrate their Japanese operations into a new global structure. In the past, companies would have worked on development plans for the whole world 'except Japan'. But those days are quickly evaporating and companies need to set out in a new direction. Japan is taking part in the trend for globalising clinical trials. Companies are working hard to leverage global operations and are quickly taking advantage of the opportunities offered by the Japanese government. Two typical approaches have emerged to address this emerging tide of globalisation. The first of these can be called, 'mirror image myopia' and the second, 'Japan-centred syndrome'. Both of these approaches are attractive at first glance. However, the practicalities of the current environment demand that companies not try for a quick-hit, generic approach but rather a customised approach that matches their global strategy. Some practical ideas are presented to help avoid common pitfalls in globalisation relative to your Japan operations. In the end, by taking a balanced, strategic approach, companies can make the most of their global operations in Japan – whether these be Japan-based or globally based organisations.

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INTRODUCTION

For many years, different standards in the regulatory and clinical trial environments have led companies to delay development – and ultimately registration – in Japan relative to the rest of the world. Although reports vary, IMS data show that only 22 per cent of the drugs launched around the world between 2002 and 2006 are available to Japanese patients and that up to 40 per cent of the world's top 99 compounds on the market at the end of 2006 were not available in Japan. Clearly there are many reasons for this

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gap – ranging from individual company strategies to wait for proof of concept outside of Japan before starting development in Japan – to significant delays caused by the need to repeat clinical trials with Japanese patients to achieve registration.

As a result, this time gap between global and Japanese registration – in many cases measured in terms of years and not months or days – is now known as the 'drug lag'.[1] This issue is being examined with a new vigour in Japan, with the attention coming from both pharma companies and three different ministries within the Japanese government: the Ministry of Economy, Trade, and Industry (METI), the Ministry of Education, Culture, Sports, Science, and Technology (MEXT), and the Ministry of Health, Labor, and Welfare (MHLW).

This dramatic shift in Japan is enabling, most importantly, specific actions to support the execution of truly global trials. These trials now seem to be taking on two different flavours. The first flavour is the 'pan-Asian' study. This involves therapeutic areas that are anticipated or demonstrated to have ethnic differences between Asian and Western patient populations. The Japanese authority is beginning to allow the use of Asian patients in trials to support registration in Japan. Such studies allow trial subjects to be drawn from a broader Asian population – hopefully helping to reduce overall trial costs. Pfizer's Tolterodine phase III trial was the first case of this strategy and successfully support Japan approval in 2006. As a result, such studies are becoming an increasingly common part of a global clinical strategy – and are helping to overcome differences in practices in Japan.

The second, and more important, flavour is the truly global trial. These studies finally include Japanese subjects as a direct part of the global, multinational trial. For example, the global study may incorporate subjects from many countries around the world – including Japan – under the same protocol and then is used to support Japan registration. The RENAAL study by Merck/Banyu was the first such trial to be successfully used in support of an approval in 2006.

Since then, many companies – such as Wyeth, BMS, Merck/Banyu, and AstraZeneca – have publicly announced that they will move to global, simultaneous development. Still others are moving strongly in this direction – even they may not have made public announcements to this effect.

And yet, to achieve this goal, companies to make several significant changes to enable pan-Asian and global trials. These include operational changes and alignments with global as well as organisational revisions. Ultimately, such changes will enable Japan development to truly become part of the global pharmaceutical industry.

TWO TYPICAL RESPONSES

Strategically, companies seem to be taking one of two generic approaches to globalise their development organisations in support of the above push for global clinical trials. In the first of these, global companies drive to create mirror images of their global organisations in Japan. While their Japan subsidiaries cannot look and feel like those in headquarters – or even main satellite countries like Germany or Canada – these companies drive to create exactly the same organisations in Japan as existing in the rest of the world. This leads to what we call 'mirror image myopia', which can lead to sub-optimisation of the Japan organisation.

In this case, historically global pharma companies develop mirror image organisations (down to functions and roles) in Japan as if the goal of their globalisation efforts were to transplant HQ thinking into Japan. As a result of such efforts, communication between global project and Japanese project teams has, indeed, improved. However, this approach also leads to the fragmentation of the Japan development organisation into the same set of functions which exists in global. For example, a medium sized Japan development organisation might have 125 or so people in Japan. Compare that with 4,000 or 5,000 in

the corporate development organisation and you can get an image of the problem. Since Japan is typically the only country aside from HQ with a full development organisation, mimicking HQ leads to functions with one or two people reporting to lower-level managers with little to no non-HQ exposure. So, while this approach is an improvement over nothing, it leaves significant opportunity left to be captured.

In the second approach, we see how a typical Japan-based pharma company might address the topic of globalisation. Here, trying to preserve the original core culture, language, and approach of the company, they continue to drive as the core as they expand globally. This leads to a 'Japan-centred syndrome', where a large Japanese pharma company will tend to insist on maintaining virtually all control in Japan. While this does afford some companies the means to launch and/or grow operations outside of Japan. Unfortunately, this ignores some basic constraints in the pharma industry today. First, it is unfortunately true that the best practices (and therefore a great majority of the related talent) in clinical development do not reside in Japan. As such, focusing on Japan creates artificial distance to the industry-leading markets of the US and EU. Secondly, this approach also limits access to state-of-the-art technology, leading scientific knowledge, and academic/industry leadership. It also limits the extent to which an organisation can truly become global.

AVOIDING THE COMMON PITFALLS

As the tide of global development comes in rapidly, some companies are breaking from the above approaches. Three companies in particular have begun to apply some emerging practices for their development organisations that should serve as good lessons. Below are the examples of companies bucking the trends described above.

The first example, 'Company A', is a Japanese company. This company has developed three regional centres of clinical development around the world. For each of these centres, the company gathers talents from around the world. In addition, the global project management organisation was spun out of the headquarters into a separate organisation to help maintain independence in managing manage global projects. This enabled three regional centres to evenly handle project leadership, and has enabled the company to avoid conflicts for and with global leadership.

The second example, 'Company B', is a large Japanese company. This company has organised itself into three regional development centres in the world: Japan, US, and Europe. Although their headquarters functions still exist in Japan, they selected a non-Japanese leader to head R&D in Japan. This has helped HQ avoid becoming too focused on Japanese process, culture, or systems – and thereby bypassing the Japan-centred syndrome. With the application of effective talent management, this company, unlike many others, has started developing truly global protocols proactively involving the three regional regulatory and medical requirements at once.

The third example, 'Company C', involves a company headquartered outside of Japan. While the company is generally viewed from the outside as being relatively headquarters-centric, it has managed to find a balance between global alignment and local productivity. This has allowed the local subsidiary to achieve best-in-class performance as measured by Centres for Medicine Research (CMR) benchmarks. For example, in establishing a system to conduct multinational clinical trials (both pan-Asian and global), this company did not insist on creating mirror image of all corporate development functions, but rather tried to align some specific global 'roles'. This enabled all regional staff to have same expectations for these key roles. Meanwhile, some of the global functions have been combined for ease of management in Japan – enabling all groups to have at least ten staff – thereby maintaining local productivity.

SOME LEARNINGS FROM THESE LEADING COMPANIES

By examining the three example companies among others, it is possible to highlight a few learnings. The following four areas described below should be considered by pharma companies taking on the task of globalising their clinical development capabilities.

Organisational structure

Corporate management makes use of organisational change as a common repair to problems. Yet those companies who do this well have learned to balance the desire for a centralised versus de-centralised organisational structure. This can also take the form of how staff in line functions – such as site monitoring or data management – report to programme or therapeutic area management as well. These two competing perspectives need to be balanced dynamically. This means that, over time, focus may start with line functions and graduate to therapeutic areas as capabilities deepen in the organisation.

Organisational design can also be used to dynamically balance the global need for standards with the need for local customisation. For example, a global organisation might handle clinical monitoring as either a local structure in many countries in order to support strong relationships with key opinion leaders. On the other hand, another company might approach this as a single, global function. In addition, if we look at more operational functions such as data management and biostatistics, one can see that the parameters for design could be driven by cost and therefore into low cost areas such as India, Eastern Europe, or South America in order to achieve true economies of scale. In the examples above, Company A made good use of this approach.

Finally, good organisational design and implementation will also enable the development of key skills. As Figure 1 shows, a mature development organisation today requires both therapeutic area (TA) capabilities as well as skills in line functions like clinical operations and data management. Ultimately, it is important to balance strong skills in both areas to get the most out of a global organisation.

Talent management

Driving global projects in a global organisation requires the right people. While this sounds trite, it is usually overlooked as management tries to find development roles for staff. This area is often linked with organisational design; however, we believe it is critical to view this separately. For example, a project leadership system that involves the proper talent (scientific, business, cultural sensitivity, project management, etc) will

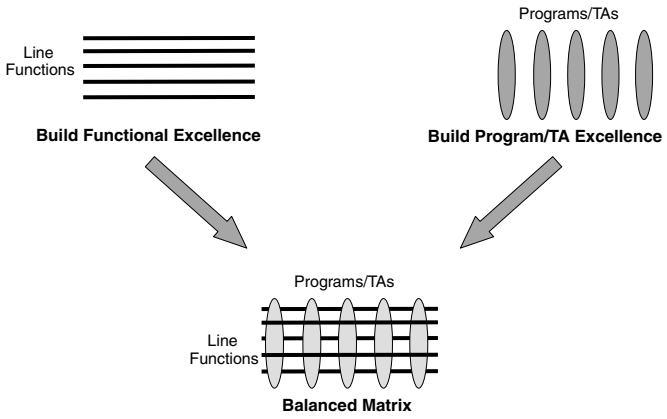

Figure 1: Building functional capabilities and therapeutic area excellence can enable a balanced matrix organisation

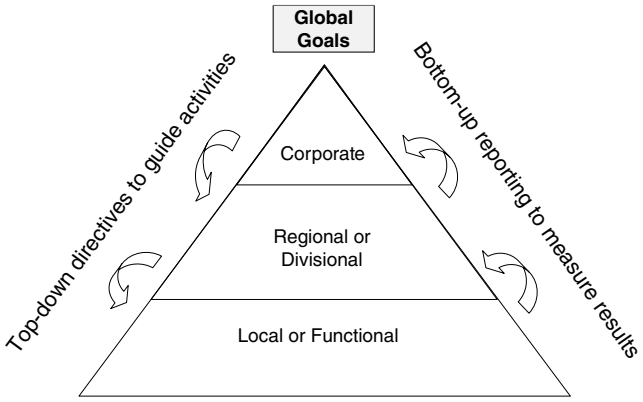

Figure 2: Use performance metrics to disseminate goals and monitor results during the integration

avoid the typical political conflicts between global headquarters and subsidiaries. It is not uncommon, for example, for a naïve project manager to make assumptions about a standard of care in another country. Thinking 'We don't need to check with Japan. This protocol is valid in many countries, it must be so in Japan', leads to significant gaps – and possibly even study failures.

In this way, one can look at resources in a global pool. Company B above did just this. As a result, leadership for global development – or even of specific trials – would not necessarily be drawn from a particular location or company headquarters. Leadership would be selected from the global talent pool and needs to be able to leverage state-of-art technologies, grasp leading scientific knowledge, and understand various regulatory requirements at the same time. True talent would not be limited by language or cultural barriers when interacting with the rest of the world. This lever can be used by pharma companies to avoid global conflicts such as that described in the Japan-centred syndrome.

Structured performance metrics

Effective measurement of a process, system, or organisation is critical to help achieve balance in a global organisation. Effective performance metrics can help maintain balance between critical performance metrics such as cost, quality and cycle-time. Such a metrics system is necessary to maintain balance in a global organisational between global and local objectives. As such, metrics should consist of globally aligned measures, regional performance numbers, and functional performance measures for each region. Effective metrics are also balanced between global objectives and regional constraints. Figure 2 shows how metrics need to be consistent from the top – or corporate level – to the bottom – local or functional level. For example, a global goal might be the number of trials completed. A regional goal could then be the number of patients in trial from the specific region, and the functional metrics would then be enrolment duration and patient numbers per protocol. In this way, global, regional, and functional performance can then be captured.

Communication/interaction

Effectively interacting with a truly global environment involves all of the above learnings. It implies active communication with the local regulators, with various investigators, and with each of a company's subsidiaries. It involves dedicated, honest, and open communication regarding key elements of programme strategy, for example. This kind of interaction is needed to optimise global clinical strategy by managing scientific uncertainty against local expectations and regulatory requirements. It is not uncommon

to hear of global pharma companies hampered by not effectively communicating with their local contacts. For example, a US-originated protocol might encounter serious setbacks in enrolment based on global inclusion/exclusion criteria. Yet these need to be well understood at the Japanese trial centres. Without a means of sensing how a protocol might be performed, problems are likely. This is especially pronounced as we enter a time of rapid increase in the number of global and pan-Asian trials.

CONCLUSION

Global clinical development has arrived in Japan. The MHLW's various announcements of public support through 2007 for both pan-Asian trials as well as for global trials which include Japanese patients as part of the global pool – both in support of registration in Japan – is a key indicator of change.

With deep changes in the clinical trial environment in Japan finally becoming a reality, global companies are taking a hard look at how they globalise their development operations – both inside and outside of Japan. They are examining how to optimise the size of their subsidiaries in Japan as they cope with global competition and constant pressures on margins.

Management needs to set forth plans to take the necessary steps to truly globalise. This means that global companies need to develop clear strategies to align their Japanese development organisations with global processes and systems while maintaining local productivity. Also, they need to maintain strategic linkage in Japan in support of their global objectives. And, while companies based in Japan are eyeing expansion outside of Japan, they need to optimise their development organisations as well. These companies need to take better advantage of global talent and resources by cantering their development leadership virtually – potentially outside of Japanese headquarters.

Some lessons from those companies who are trying unique approaches should be helpful for those considering globalisation. There are no easy solutions. But management can truly make a difference by taking a measured approach in accordance with their corporate strategy – rather than trying for a quick win.

Note

1. 'Drug-Lag' – This is the time difference between drug approvals outside of Japan and inside Japan. The Office of Pharmaceutical Industry Research reported in May 2006 that this currently averages about 3.9 years – from first approval in the first country in the world to approval in Japan.