

# Managing Clinical Logistics for Clinical Trials in Emerging Markets

Emerging markets for clinical development typically encompass Latin America (Argentina, Brazil, Chile and Mexico), Eastern Europe (Russia, Poland, Ukraine, Hungary and other CEE countries), Africa, China, India, and Southeast Asia. Another definition sometimes used for an emerging market for clinical development is any country that is not part of the three International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) regions, although given the closer alignment with ICH undertaken by certain emerging countries, such definition can be somewhat misleading (especially since some of those emerging countries are now part of the European Union and follow ICH). According to PAREXEL's Bio/Pharmaceutical R&D Statistical Sourcebook 2008/2009, patient recruitment in countries like Poland or Mexico can be twice as fast as the United States, for instance. Some of the factors contributing to emerging regions' recruitment efficiency include large patient populations who are eligible to participate in studies involving major therapeutic areas, as well as a high number of physicians including trained clinical investigators. In addition, clinical trials in countries like India and China can cost less than half what they would cost in Western Europe or in the United States.

Although the potential for cost savings varies by country, this is certainly a noteworthy consideration. Due to these factors and others, emerging markets have been continuously gaining the attention of the biopharmaceutical industry, and managing clinical logistics in those regions has become a key ingredient of success for clinical trials.

Effective clinical logistics in emerging markets is not, however, a straightforward outcome and requires focused expertise. To start, most emerging countries have included selected regulatory variances on ICH and Good Clinical Practice (GCP) guidelines. Additionally, the clinical logistics approach selected by sponsors can have significant cost and time implications. Finally, leveraging appropriate clinical logistics training, resources and experience is paramount to a successful clinical trial execution.

As far as clinical logistics are concerned, most emerging countries have regulatory differences: drug import regulations incorporate a number of country-specific aspects, labelling requirements differ from country to country, and biological specimens are subject to different requirements or formalities.

As explained in Good Clinical Practices: A Question & Answer Reference Guide 2008, the drug products used in the clinical trials in China, for instance, must be submitted to the National Institute of the Control of Pharmaceutical and Biological Products (NICPBP) to be assayed. The NICPBP's role in that process is to check the technical data and to perform the specification verification of new drugs before the registration and approval by the State Food and Drug Administration, P.R. China (SFDA). Without the certificate of analysis issued by NICPBP, the Institutional Ethics Committee (IEC) will not approve the clinical study. Combined with the fact that all

clinical trials in China must be conducted in SFDA-approved sites, i.e., sites that obtained a certification from the SFDA to conduct clinical trials, regulatory-compliant logistics can be very specific, starting with the initial sample logistics.

One of the challenges in working with emerging countries is the need to keep track of the many regulatory evolutions that can occur. Mexico is a country where clinical trial activity has flourished, like in many other emerging markets. According to the Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS), local clinical trial activity rose from 285 protocols in 2000 to 1,360 protocols in 2007, a 25 percent

compounded annual average growth. According to Frost & Sullivan, to cope with such a growth, Mexico has undertaken a number of initiatives to improve its regulatory framework, including the creation of a permanent pharmacovigilance programme and the enactment of a Mexican Norm. Amongst other evolving factors, norm 4.3, part of Mexico's importation regulation that waives the requirement for an import licence for study drugs with non-commercial value, went out of date in February 2008. In transitional situations like these, sponsors and clinical trial supply specialists need to continuously monitor regulatory evolutions when managing shipments into Mexico. Clinical Research Organizations (CROs) with a local presence have a clear advantage in that they understand the regulatory environment and specifics of the country. In fact, those CROs that have long-standing experience and infrastructure, such as a contracted local drug depot or even their own local drug depot, can better help sponsors navigate the logistical uncertainty resulting from regulatory changes. A local depot, for instance, allows the sponsor to store medication and supplies and thus lower the risk of delays due to the import process.

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In Chile, a country that presents advantages for seasonal medication with its inverted seasons compared to United States and Europe, importation regulations require a special certificate: Autorización de Uso y Disposición, also known as UyD. First, an import licence needs to be obtained from the Instituto Nacional de Salud (ISP) – it is required for all Phase I to IV clinical trials and approval takes around 3 weeks. The Import License is the document presented to the ISP in which the detail of IMP materials is declared (presentation, concentration, active ingredients, etc.), which allows the overall import of IMP materials for already approved clinical trials. Approval of the UyD certificate normally takes about a week after IMP materials have made their entry into the country through customs, and it results in an authorisation for drug use, assuming previous registration.

As those few examples show, drug import regulations vary by country in emerging regions, and managing clinical logistics in this context requires local monitoring of import regulation evolutions in addition to local logistics expertise. Similarly, from a GMP perspective, labelling requirements vary from one country to another.

China, Taiwan and Hong Kong, for instance, each have their own regulatory framework, infrastructure and approaches. Whereas in Taiwan the Clinical Trial Certificate and Drug Import Permit are granted at the same time, Hong Kong requires three more days after the Clinical Trial Certificate is granted. And China's process is typically a lot longer than Hong Kong or Taiwan, sometimes making that country difficult to keep in the clinical study. Despite the Chinese commonality, there are differences, including for drug labelling, that can significantly affect clinical logistics.

Based on Good Clinical Practices For Clinical Research In India provided by the Central Drugs Standard Control Organisation, the label should necessarily contain the following information: the words "For Clinical Studies only", the name or a code number of the study, name and contact numbers of the investigator, name of the institution, subject's identification code. In addition, the manufacturer would be listed on the study drug label, so the drug can be traced to the specific manufacturer.

South Korea has been using ICH-GCP since 2001 and is thus another emerging country well-suited for global clinical trials, especially as it introduced separate processes for Investigational New Drug (IND) versus New Drug Application (NDA). South Korea does not require a drug import licence for clinical trials and has been opening clinical trial opportunities over the last few years. Nevertheless, there are specific translation requirements that should still be considered when doing labelling for sites in South Korea.

While label requirements change from one country to another, this does not necessarily mean that drugs always need to be allocated on a country-by-country basis. For instance, it is important to work with booklet labels that meet the labelling requirements of several countries at the same time. While these are typically more complex to check from a design and production perspective (amongst other factors, you need approval for all the countries covered by the booklet label), they enable sponsors to reduce the drug overage that would otherwise be required.

Laboratory sample management is another aspect of regulatory

differences that affect clinical logistics. Biological specimens and related supplies are indeed subject to different requirements or formalities, depending on the emerging country. Many countries, including Taiwan, China, the Philippines and Thailand, have different regulations concerning biological specimens. As sponsors plan for a study and study sites locations, they should engage in discussion with their internal logistics department and their external clinical logistics provider, as to the implications and considerations related to laboratory analyses and associated logistics.

For instance, a permit for laboratory kits is required for Taiwan, Thailand, Indonesia and Vietnam, plus South Korea and Taiwan require permits for some devices. China restricts the exportation of whole blood and genetic materials. The Philippines require a declaration of non-infectious material by the clinical investigator. Thailand requires a material transfer agreement to be signed between the site and the laboratory.

In India, sponsors who intend to export human biological specimens from India for test purposes must apply for export permission from India's Director General of Foreign Trade (DGFT). Blood products are generally classified as restricted from an export perspective.

As these examples show, export of biological specimens can be restricted or even prohibited. Familiarity with the requirements and process is critical and some aspects should be considered upfront in the study design.

The many regulatory differences and their evolution implied by the spectrum of clinical trial emerging markets in which to conduct clinical trials clearly emphasise the need for growing clinical logistics expertise as those regions of the world themselves grow in importance. Import regulations, labelling requirements, and human biological specimen regulations are all very telling examples of such expertise.

In addition to the regulatory compliance requirements, another facet that makes clinical logistics critical is the significant impact a clinical logistics approach can have on cost and times for study conduct. Such clinical logistics approach should start with the study protocol, include IMP manufacturing aspects, and evaluate drug valuation. Russia, Brazil and Chile provide great examples of why the clinical logistics approach should start with the protocol.

Russia, for instance, lets you import only enough drugs for the expected number of enrolled patients in Russia, taking into account what is portrayed in the Ministry of Health (MoH) approval. The quantity of IMP has to match the number of patients declared in the MoH approval. The authorities will verify based on the protocol if the numbers match. As a simplistic example, if 10 patients are expected to be recruited in Russia as declared on the MoH approval and if, based on the dispensation schedule, a patient is supposed to take 5 doses of treatment type A throughout the study, then the import licence should contain 50 kits of treatment type A. This simplistic example obviously does not cover the wastage due to stratification factors, broken kits, non-enrolling sites, etc. Therefore, a clear algorithm should be provided for the calculation of the quantities of IMP. However, since a sophisticated randomisation algorithm might be challenging to understand or to convey to custom officials, an alternate approach would be to declare a higher number of patients

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on the MoH approval to come to an acceptable number of IMP. This might at any rate be a preferable and more conservative approach given recruiting uncertainties and given the other stratification factors mentioned above. This approach may sometimes be counterintuitive to some sponsors, who prefer to under-estimate the number of patients in the protocol. One of the downsides of using a conservatively high number of patients in this specific case is that such a number usually results in higher costs for patient insurance, costs normally paid back when unused.

This Russia example is one that emphasises the advantages of clinical logistics integrated with clinical research operations, as input can be provided by the logistics team to the clinical team before Clinical applies for MoH approval locally in Russia.

Another example is Brazil, which requires a quantitative estimate of the drugs and products that must be imported to a clinical site in the dossier submitted to Agência Nacional de Vigilância Sanitária (ANVISA), Brazil's regulatory agency.

In Chile, beginning in October 2008, quantitative estimates of drugs and medical products (e.g., syringes and certain medical devices) for the overall study will also be required. These quantities can be modified (modification of Import Licence) in case the initial estimate was wrong. There is an assumption that the process already in place for IMPs will thus be applied to other medical products. At the moment, considering that this will be a new norm for medical products, there is still some uncertainty on the future processes.

It is useful to evaluate clinical logistics as aspects for emerging markets at the protocol stage. This is one of the reasons why integrating the clinical logistics team with other clinical research functions can be advantageous. Manufacturing aspects are another important consideration since they influence the expiry date and stability of the IMPs. This is especially true of biologics.

As another example of emerging market practical necessities, in India it is important to consider the residual shelf life upon import for imported medications. For the import of drugs for marketing in India, drug regulation rule 31 stipulates that the "licensing authority shall not allow the import of any drug having less than sixty per cent residual shelf-life period as on the date of import". While clinical trial samples are not subject to the same requirements as imported drugs for marketing, it is important to take into account such practices, expectations or even regulations in certain cases. Such practices can also avoid unnecessary re-supply requirements with later expiry dates. This is in addition to the traditional requirements that the drug be manufactured in accordance with GMP and packaged appropriately to reflect trial requirements (e.g., binding, labelling, storage, etc.).

Schedule Y refers to requirements and guidelines to be followed in order to attain permission importing and/or manufacturing new drugs to market or to undertake clinical trials in India. Once written approval of the Schedule Y application is obtained from the Drug General Controller of India (DCGI) and an IEC, a clinical trial may be initiated. In order to ship products from other countries, however, a separate import licence is required: a T-Licence, as in Test license, for

IMPs. A T-Licence is normally valid for one year and for multiple shipments; it can be, and would logically be in most cases, submitted together with Schedule Y.

Regardless of the countries, the quantity of IMP made should align with the strategy used for clinical logistics, especially as it relates to drug depot versus direct-to-site distribution. Drug depots make sense when labels or label booklets can address a high number of countries and sites and thus reduce drug overage through consolidation, when there are exacting shipment, import, insurance and custom requirements making consolidated shipment and clearance advantageous, or when the drug supply is limited or otherwise very expensive. Also, for some countries, shipping directly to site is simply not allowed or practical.

Another aspect of the clinical logistic approach that can have a significant impact, in addition to protocol or manufacturing, is the valuation used for IMPs. Let us look at the situation in Ukraine, for instance. Clinical trials in Ukraine are conducted in accordance with the ICH GCP requirements. Regulations for performing clinical trials

are provided by the Ukrainian Law on Medicines of 1996 (amended in 1997 and in 1999). To import investigational drugs into Ukraine, the taxation agency estimates the price the medication would command, if it were a product marketed in Ukraine, and then charges a commensurate importation tax. When importing drugs marketed in Ukraine (even if they will be used for clinical trials), the price in Proforma Invoice should be close to the market price in Ukraine (to avoid any problems with the Tariff Department). When importing drugs, which are not marketed in Ukraine, the price of the drug in the Proforma Invoice should be close to the price of marketed analogue. In a recent endocrinology clinical trial, for instance, the sponsor ended up using a proforma value of \$30 USD for Ukraine, whereas the value before such

considerations was \$5 USD. In addition to other more complicated import cost considerations linked to transportation costs and VAT, the customs fees depend on the type of import (different percentages being applied to the proforma value for IMPs, laboratory kits, printed materials, or medical devices to calculate the custom duty).

Managing clinical logistics in emerging markets thus requires upfront strategic thinking from the protocol stage, involving aspects such as patient enrolment figures, IMP shelf-life, as well as drug valuation. All those emphasise the expertise factor endemic to managing clinical logistics in emerging markets. Another emerging markets requirement for success is leveraging appropriate clinical logistics training, resources and experience. Such operational aspects include the training of investigators, the actual management of drugs and biological samples, as well as key study enablers.

It is important to leverage on-the-ground local presence and to start clinical trials with training of investigators on the drug and biological samples processes right upfront during investigator training. This enables an effective clinical trial logistics system, which is critical, especially in emerging regions where investigators may not always be as familiar with such processes.

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A simple presentation and clear approach to clinical logistics can go a long way in avoiding subsequent clinical logistics related issues when the trial is up and running. It is important that clinical site personnel know what to do when receiving drug shipments, understand storage requirements (and validate that such requirements are indeed available on site!), and comprehend the steps involved in re-supply or return of drugs or ancillary supplies. Proper access to, and trained utilisation of, a clinical trial Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS) is essential, at least for large trials. Such training will enable drugs to be made properly available to the clinical trial after receipt or for proper quarantine procedures to be used, if there were an issue with a drug shipment. Similarly, site personnel need to understand process, tools and forms available for biological samples.

Experience and on-the-ground resources can also be extremely useful to manage shipments. Many aspects of clinical trials require endemic and local knowledge. For instance, courier companies that perform well in a given country do not necessarily have the same performance in another region. Similarly, not all contracted drug depots are created equal – notwithstanding pricing, some have better quality, personnel and performance. Such practical experience and insights will be critical in deciding which locations to use. Given Quality Person (QP) release requirements in the EU, it will be common in a global clinical trial for the main drug depot to be located in Western Europe. Similarly, given the accounting required for local purchasing of comparator drugs and the resulting total cost of ownership, a central procurement approach makes sense in many cases, although there can be exceptions. While standard operating procedures and strong sourcing capabilities certainly help, many such decisions also come from experience and practice.

Integrating laboratory forms, laboratory kits and laboratory-related instructions with the overall approach is helpful in simplifying clinical site operations. It is important to integrate a logistics approach, the analysis provided by third-party laboratories, the clinical operations and site contacts to ensure a more proactive clinical logistics approach, more efficient closing of queries and better clinical trial data. This effective approach enables sponsors to benefit from efficient processes without bundling pass-through laboratory analysis costs with clinical logistics services.

One last aspect that is important as an operational perspective is using the right tools in the right way. For instance, when possible, randomisation used in IVRS should typically be by site rather than by region or country. The choice of stratification factors is normally the result of consultations between the study statistician, medical and clinical. It can have a huge impact on clinical logistics, especially in large studies where a lot of depots have to be used due to the local requirements.

Randomisation balanced at the site level is the most convenient from a drug supply management perspective. Stratification at the country or study level requires a higher medication coverage that should be taken into consideration when planning the study drug demands. The consequences of country or study stratification are that at the same site there may be successive randomisations to the

same treatment arm. This may require maintaining higher medication stock at the sites to avoid randomisation failures.

Similarly, the consequences of study stratification are that within the same country, the majority of the patients might be randomised to the same treatment arm. This may deplete the depot stock for that particular treatment arm far sooner than expected and generate logistics difficulties when preparing a new depot shipment and dealing with import licences.

As far as tools are concerned, using the right forms is often an overlooked issue. However, having smart form designs can have a significant impact on whether they will be filled out properly. There is value in using proven designs. For instance, it turns out to be helpful to have a clear delineation in an Investigational Product Order & Receipt Form, determining which part is to be automatically populated by the IWRS system, which part should be completed by the Pharmacy, and which part should be completed by the Investigator. Such tailor-made solutions can prevent the loss of

samples, materials or data due to less experienced site staff.

Finally, for laboratory data management, specific tools are used for close sample identification and tracking, to prevent sample loss due to underdeveloped courier networks and lack of established procedures in certain geographies. These can be combined with online data management and data cleaning to guarantee high quality laboratory results.

In conclusion, effective clinical logistics in emerging markets are far from simple

and can require significant expertise. Successful clinical logistics in emerging markets require a strong understanding of evolving regulatory environments, an involvement in study design and setup, starting with protocol design, as well as the benefit of past experience and battle-tested processes and resources. Given the interactions with regulatory and clinical operations, clinical logistics for emerging markets are best managed when they are closely integrated with other clinical research resources. Ultimately, a suitable clinical logistics team can deliver significant value to sponsors in terms of cost avoidance, compliance with regulations, process and time efficiencies, as well as increased flexibility in responding to changes in requirement – all of which can have a significant impact when managing clinical trials in emerging regions ■

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