Cromos Pharma's update on drug registration in Russia

The number of active clinical trials in Russia has increased significantly during 2012. Much of this increase can be been attributed to new regulatory requirements put forth by the Russian Ministry of Health (MoH) which went into effect in September 2010. This "Circulation of Medicines" law affects both domestic and international pharmaceutical manufacturers in very significant ways. For international firms intending to market its products within the Russian Federation, undoubtedly the most important provision is a new requirement wherein Russian patients must be included in the company's pivotal phase III clinical trials. Assuming that the aforementioned Phase III trials have not already been completed, this requirement can be met by one of two mechanisms: (1) enrollment of Russian patients in trials that are yet to be undertaken; or (2) under circumstances wherein an international treaty(s) exists between Russia and another country (or jurisdictional authority) that provides for mutual exchange of clinical study data, there may not be a statutory need to conduct one or more domestic registration studies in-country. In the absence of the two qualifying conditions as stated above, the most direct and expeditious route leading to the right to market and sell Pharma products within the Russian Federation is to repeat a properly designed and powered registration trial using Russian subjects.

Based on our collective experience from the past two years, it is now clear that the option of adding Russian subjects to an already ongoing pivotal trial is more cost-efficient and more expeditious than conducting an entirely new registration study. Due to the ambiguity of this new legislation and lack of guidance from the MoH, it has taken the pharmaceutical industry more than a year to realize the value of this approach. In light of the estimated size of the Russian commercial retail market for Pharma products of $18.7B in 2010,[1] and the projected CAGR of nearly 16% for the next several years, the total Russian market for Pharma related products is expected to reach $31B by 2016[2]. Given the size and growth of this market, it is clear that the most important strategic consideration by international Pharma companies is to comply with the "Circulations of Medicine" legislation in a manner that is timely and that leads to an indisputable regulatory outcome. As this new regulatory requirement was unforeseen as recently as two years ago, these efforts represent new and incremental costs for Pharma's clinical development and regulatory budgets. The strategy selected must therefore provide the sponsor with the best possible return on these incremental development costs. The remainder of this paper is dedicated to providing timely guidance and prospective scenarios by which an international Pharma company can identify a registration strategy that is both cost-effective and with minimal risk with regard to the review process that will ultimately be conducted by the MoH.

There are three scenarios that must be considered when establishing a registration strategy for a product intended for marketing within the Russian Federation.

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1 http://pharma.about.com/od/Sales_and_Marketing/ss/Top-Emerging-Pharmaceutical-Markets_4.htm

2 http://www.slideshare.net/Shepherd12/russia-pharmaceutical-market-summary#btnNext

Scenario No. 1: the candidate drug has not yet entered pivotal trials

Depending on where the drug is in the clinical development process, this scenario has been shown to be the most favorable in terms of achieving a favorable regulatory review that is both cost-effective and expeditious. The commitment by the sponsor to include Russian subjects in a pivotal study that has not yet commenced has been shown to have the least risk of an unfavorable review by MoH authorities. In this situation, we recommend to all of our sponsors that the commitment to include Russian subjects in the drug development plan be communicated to the MOH as early as practically possible. In that regard, the reluctance that international sponsors have had in the months following enactment of the Circulations of Medicine law to pursue this avenue was arguably ill-advised, although understandable. It has been our experience since 2010 that remediating the product registration strategy to include Russian subjects can be achieved both quickly and at modest cost. That being said, the approach used by the sponsor to achieve this outcome is critical. Involvement of a regional or local CRO should be strongly considered. As a practical matter, we extend this recommendation to sponsors that have their own in-country clinical development staff. The return-on-investment (ROI) and time-to-completion that can be achieved using local CROs that have a track record for managing registration studies of this type is compelling. Clearly, with regard to those sponsors that lack in-country clinical development resources, it is equally advantageous for them to select a local CRO partner with experience in conducting these rapidly moving extensions of the sponsor's clinical development program. Regardless of whether the sponsor possesses internal clinical development resources, a final and important consideration when choosing MoH registration strategy is to recognize that Russia remains a country whereby personal relationships and prior history often provide the final assurance that the MoH decision-making process will result in a positive and timely outcome for the product's future commercial success.

If a CRO for the pivotal trial has not been selected, the company should look for the CRO that is well represented in Russia. A word of caution - many CROs claim to have strong local presence when in fact this is simply not the case. We recommend verifying the level of such presence. Some CROs may state that they have a "strategic partner" in Russia. The onus is upon the Pharma company to determine how real this partnership is and whether they can truly depend upon the partnership to support the studies that are planned. This is an exercise in risk management. The sponsor's clinical team should inquire about the number of studies that this CRO has conducted with their local counterpart, whether they have undergone a thorough qualification audit and whether the partner uses the same set of SOPs as does the lead organization. Of particular importance is for the sponsor to review the chain of communication and reporting that is to be used between the contracted organizations.

A second option would be for the Pharma company to engage a global CRO with established local presence. This alleviates the issue of data flow harmonization, simplifies reporting and accountability and makes the life of company's clinical trial manager easier. One of the downsides of this second approach is a significantly higher price tag. Based on the most recent analysis, the cost of the "Russian part" of a typical late stage trial is 40-50% higher when a global CRO is selected. As a prudent exercise in cost-containment, the sponsor must determine whether the global CRO partner brings sufficient advantage, if any, to the study or drug development program in

question. There is also an issue of timelines and responsiveness. While official data are lacking, our experience strongly suggests that global CROs have significantly longer submission delays. The reasons are simple - you are more likely to use a skilled manager to submit your second trial application this month than if it was your 20th. For the same reason, you are less likely to be upset if it is your 20th application that is delayed or rejected. Personal accountability and stake of local CROs go a long way.

Below we discuss the issues that Pharma companies face when considering the degree of its local clinical engagement.

Scenario No. 2: the pivotal trial has already commenced internationally but Russia has not been included in the marketing strategy

In this situation, we recommend immediate addition of a Russian site(s). How to proceed would depend on the way the trial was launched. If a CRO is already involved, then the aforementioned questions apply - does it have local presence? Can it reliably and quickly add local sites? Speed of initiation becomes the most critical factor in this scenario. Hence, it is important that the sponsor demand relevant metrics from the proposed CRO partner that affirms their track record for getting timely regulatory approvals.

If the selected CRO has no presence in Russia, reliance on its selection of a local partner involves risks that most sponsors would simply regard as unacceptable for their program. Close examination often reveals that the drivers and objectives for their new "partner" may differ significantly from those of the Pharma company itself. I certainly do not need to remind this audience that it is much more expensive to remediate trial-related failures than to avoid them in the first place!

If the study is being run internally, then selection of a local vs. global CRO should be weighed very seriously. In this situation selection of a regional/local CRO may be more practical. The advantages include intricate knowledge of the local clinical trial market, of its regulatory hurdles, as well as personalized approach and cost efficiency.

Scenario No. 3: one or more pivotal trials have already been completed or it is simply too late to add Russian site and subjects

According to the current Russian legislation, the sponsor must conduct an additional trial to support its NDA submission. While this sounds onerous, there are strategies by which this scenario can be managed in a relatively timely and cost-effective manner. Again, with regard to the expectations of the MoH, the details relating to what kind of trial the regulatory agency expects remain vague. The two most important questions relate to how large must the trial be and How should it be powered? Based on experience of the last two years, the Russian MoH, doesn't expect a duplication of a pivotal international study. A smaller, less stringent study is usually sufficient to serve the purposes. While it is never verbalized, the regulators do understand that a full scale trial is nearly impossible to implement. In essence, the required trial is a formality and the

decision on the approval of the drug always stems from the clinical data that Pharma company has already submitted to FDA and/or EMEA.

What becomes paramount in this setting is the ability of the selected CRO to negotiate the protocol details with the Ministry of Health. These preliminary consultations would to a large extent decide if the trial gets the approval or if it is sent back for revisions. When the trial is completed, it is also important to make sure that the submitted results fully satisfy the Ministry's requirements. Without sounding biased, in this situation we strongly recommend selecting a local CRO. The pros of this recommendation have been discussed above.

What should be the extent of Russia's involvement in a pivotal trial?

Clearly, many factors will determine the answer to this question. As our discussion centers on strategies that should lead to drug registration, we would like to make light of the following. Today Russia's regulatory guidelines do not specify the number of sites or the number of patients that have to be recruited in order to satisfy the requirement and allow submitting of an NDA. Clearly, enrollment of one patient is not sufficient. However, our consultations with the representatives of the regulatory agency could not shed light on whether 10, 50 or 100 patients would be enough.

When the sole goal is to add Russia for submission purposes, selecting one or two centers with high recruitment potential should be sufficient. This scenario also fits well when the disease entity is of a rare kind or when treatment itself requires sophisticated equipment, diagnostics or monitoring modalities. This is also a suggested scenario for the clinical programs that have already been initiated. It is worth mentioning that historically, addition of Russian sites for study rescue has been very successful. Clearly, due diligence and feasibility should be performed before this decision is made.

If the trial is still in the planning stage, then a broader decision may be at hand. In many cases, incorporating a larger number of sites may be of value. Selecting a reliable local partner that will be transparent in its analysis of recruitment potential and anticipated difficulties that may arise during the trial conduct is essential. For many indications, Russia is unsurpassed in its recruitment potential and does provide very high quality data.