

## Emerging Markets: Central & Eastern Europe

### Development and Submission strategies for pharmaceutical registration

Development strategies in CEEC – markets where clinical development is conducted prior to submission

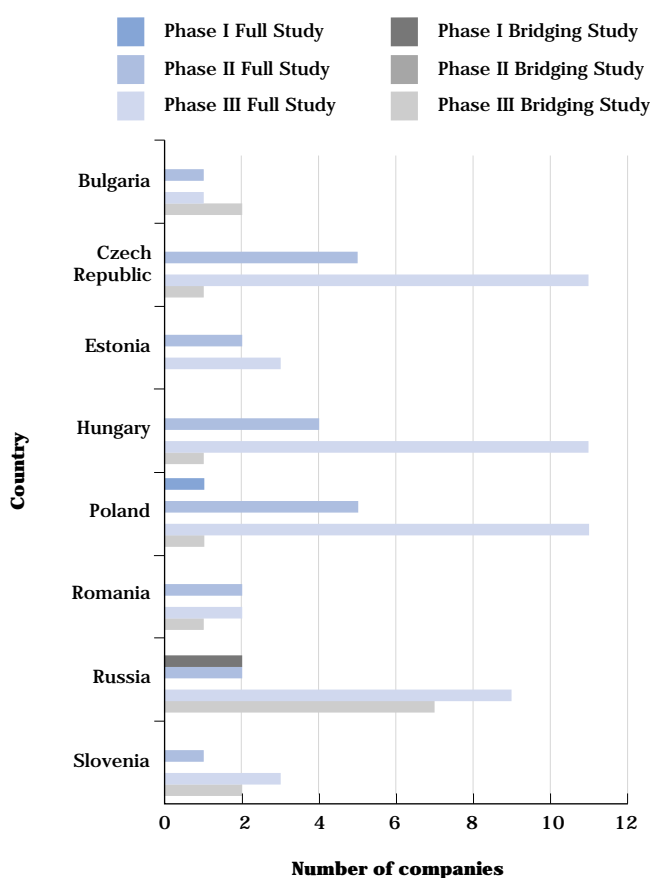


Figure 1 Markets where clinical development is conducted prior to submission. Generally, those companies that conduct clinical trials in CEEC prior to submission restrict these trials to the commercially most important markets, namely the Czech Republic, Hungary, Poland and Russia. Where trials are conducted, they will generally be full Phase III studies, which would be used in a pivotal clinical development package for submission to ICH regions.

- ❑ *The emerging markets of Central and Eastern Europe offer considerable potential for pharmaceutical investment and growth. However, diverse regulatory systems and requirements between these markets can create significant obstacles to efficient development and registration of new medicines.*
- ❑ *Considerable delays to submission may emanate from the requirement for locally generated clinical data or a Certificate of Free Sale from the source country. The need to provide samples and packaging during the review, lack of regulatory transparency and difficulties in ensuring confidentiality of the data submitted are further barriers to rapid registration.*
- ❑ *These problems, coupled with the lack of regulatory harmonisation between markets in the region, are among the major issues of concern to the pharmaceutical industry.*
- ❑ *Based on these findings, generated in a questionnaire based survey in 1998 among 25 companies, CMR International advocate building a better understanding of regulatory requirements across the region and increased communication between industry and regulatory authorities.*
- ❑ *Since this survey was carried out, a number of regulatory authorities have begun to address some of these issues.*

## Perspective

Increasingly, the emerging markets of Central and Eastern Europe, Latin America and Asia offer enormous potential for growth in pharmaceutical sales. These markets are of critical importance to the future success of pharmaceutical companies and yet considerable hurdles must be overcome before a new medicine achieves marketing approval.

To gain insight into the difficulties encountered within these three regions, CMR International conducted a survey in 1998 to identify:

- Companies' current strategies for registration, and development, of new active substances in these markets;
- Factors inhibiting timely and successful registration.

This R&D Briefing presents data for Central and Eastern European countries (CEEC) gained from questionnaires returned by 25 of the 48 companies approached. Of the eight markets considered, seven are part of the group working towards EC membership, namely Bulgaria, the Czech Republic, Estonia, Hungary, Poland, Romania and Slovenia. The final market, Russia, remains one of the largest in the region.

## Clinical development

Clinical trials are carried out in all markets of the region (*Figure 1*), particularly those of greatest commercial importance (Czech Republic, Hungary, Poland and Russia). Most are full studies conducted during Phase III of clinical development. Often these studies are pivotal to the company's global development plan for submission in other world markets, and as such reflect the quality of clinical research conducted in the region.

In most cases, trials in these markets are initiated to take advantage of local expertise in the clinical discipline concerned or to provide local physicians with experience of the product before marketing (*Figure 2*). Additionally, in Russia studies are conducted in response to requests from the regulatory authority for data from local trials.

## Submission strategies

A single strategy for simultaneous submission to all major markets in the region is the current approach of 10 companies, while some have separate strategies for each market and yet others adopt case-by-case or non-standard approaches. A large majority are aiming

Development strategies in CEEC – reasons for conducting trials in local markets

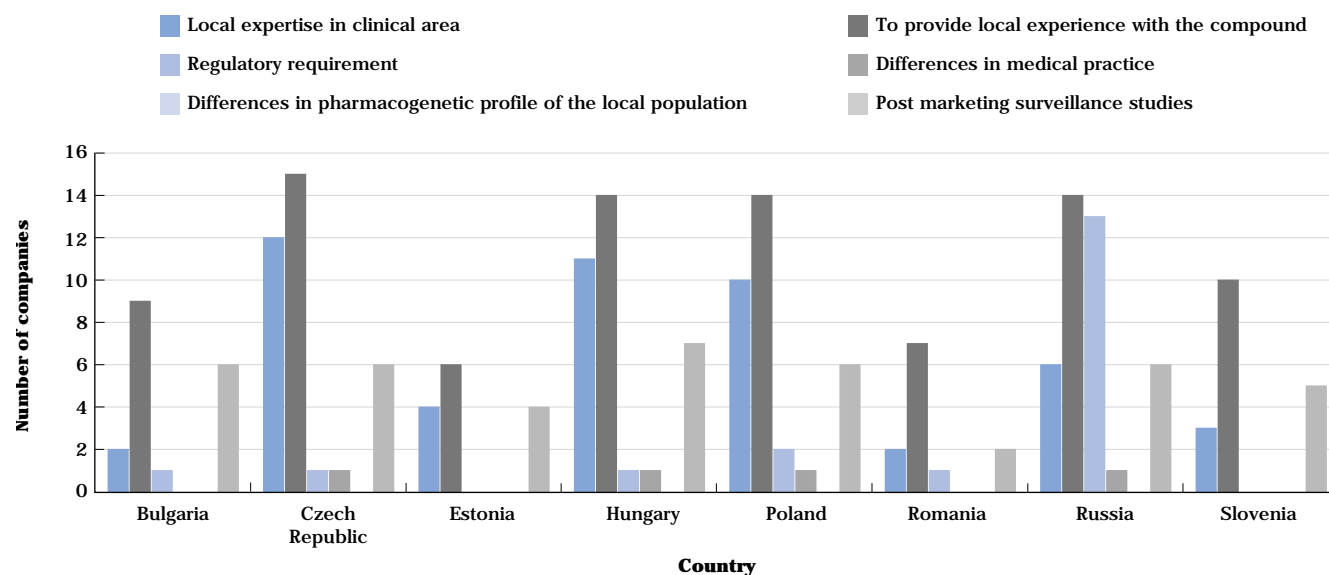


Figure 2 Reasons for conducting trials in local markets. In the majority of cases, local trials will be conducted to take advantage of local expertise, or to provide local clinicians with experience of the compound. In Russia, however, trials have also frequently been conducted in order to meet local regulatory requirements. In all countries, some companies will conduct post marketing safety studies.

## Submission strategies in CEEC – timing of requirement for CFS in local markets

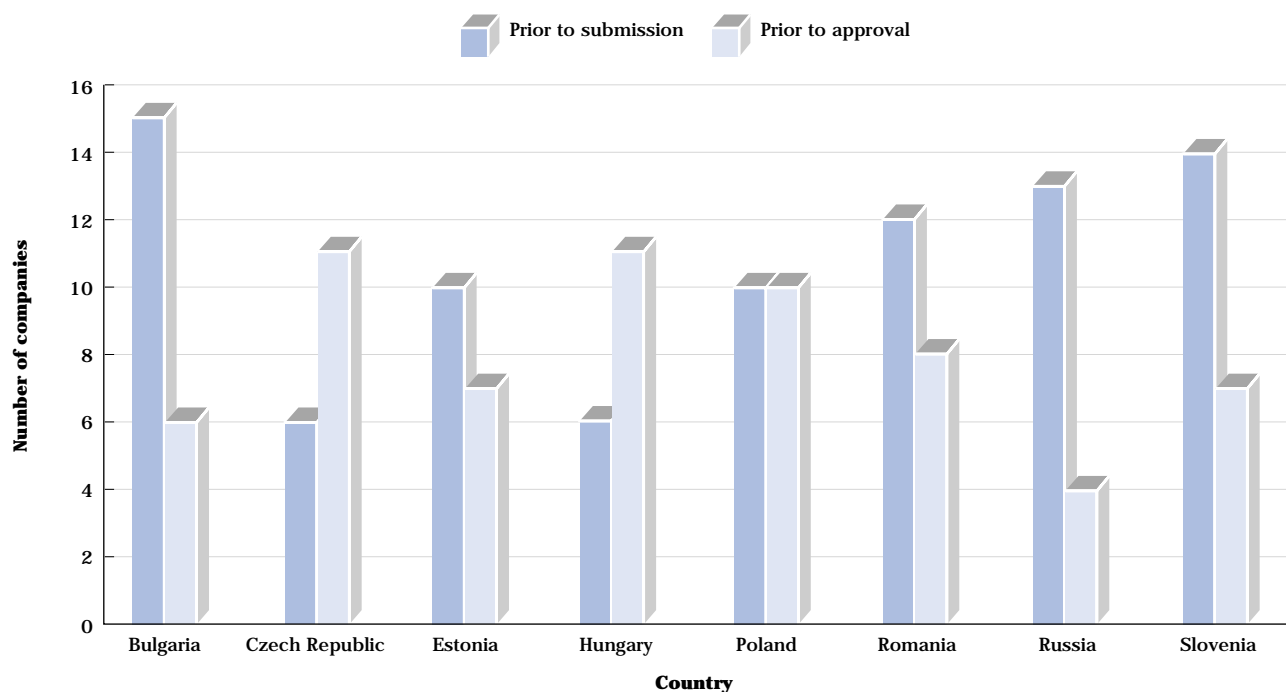


Figure 3 Timing of the requirement for a certificate of free sale (CFS). There was a division between companies who had experience of being able to delay submission of a CFS to the local regulatory authority until just prior to approval, and those that believed, or had been requested, to provide the certificate at the start of the licence application process.

to develop a single strategy for the future. Current initiatives in most of these markets to harmonise regulatory requirements in line with EC legislation will aid this objective.

Prior to submission in CEEC, nearly all companies have already submitted the dossier in the EU, and 60% have also submitted in the USA. Even so, the requirement for a Certificate of Free Sale (CFS) to be included in the marketing authorisation application can cause considerable delays (of between nine and thirteen months). The experience of companies in being able to postpone providing the CFS until immediately prior to approval is shown in *Figure 3*.

A number of companies managed to make submissions to markets in CEEC within 12 months of a submission to an ICH (International Conference on Harmonisation) country. This suggests that the emerging markets of Central and Eastern Europe are being incorporated into companies' core development programmes.

### Local experience

Within the commercially important markets, the regulatory authorities of Russia and Hungary appear to be working most efficiently in terms of granting marketing approvals, having approved 99% and 81%, respectively, of submissions made to them between 1996 and 1998. The corresponding figures for the Czech Republic and Poland are around 60%.

In addition to lengthy review times, companies experience a number of other difficulties which can become barriers to rapid registration in this region (*Figure 4*). A particular problem within the emerging markets of CEEC is the requirement for samples and packaging to be provided to the regulatory authority during the review. A further issue of concern to the industry is the need to provide, pre-submission, a Certificate of Free Sale. The success of some companies in negotiating a delay in the provision of a CFS (see *Figure 3*) suggests a potential starting point for changes in this area.

## Experience with MAAs in CEEC

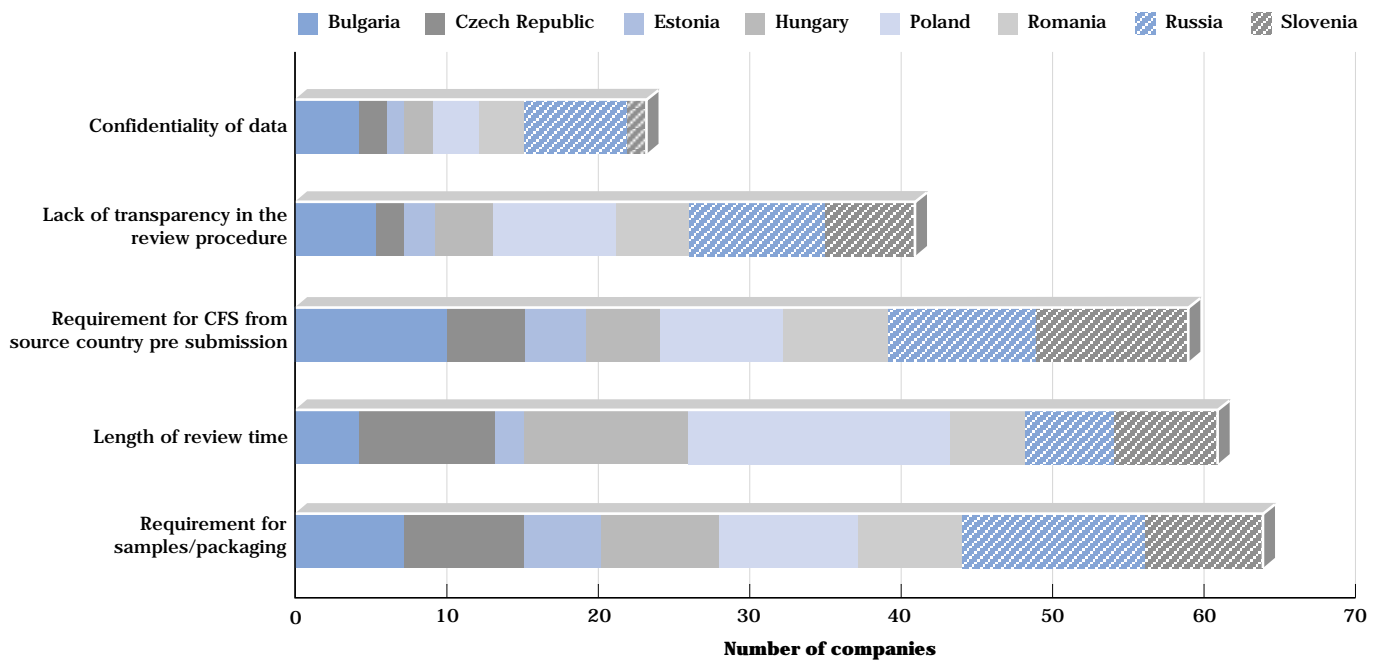


Figure 4 **Major barriers to rapid registration.** Participants were asked to identify, from a list of factors, which caused them problems when registering new drugs in Central and Eastern Europe. The issue that arose most often was the requirement for samples and packaging to be provided to the regulatory authority during the review, followed by length of review time and the requirement for a Certificate of Free Sale to be made available prior to submission.

**Lack of transparency during the review process, and difficulties in ensuring confidentiality of the data submitted, create further hurdles in the bid to achieve rapid marketing authorisation.**

### Steps for the future

**For pharmaceutical investment and development in Central and Eastern Europe to continue and grow, a**

**number of issues must be addressed. To this end, it is recommended that:**

- **better understanding of the basis for regulatory requirements, and**
- **increased communication between industry and the regulatory authorities**

**will facilitate a trend towards more efficient and consistent regulatory reviews. These in turn will assist the industry in harnessing the potential of the region.**

Copies of R&D Briefings are available on the CMR International web site.

[This Briefing on the Emerging Markets is part of a series of three briefings on Asia \(No 24A\), Central and Eastern Europe \(No 24B\) and Latin America \(No 24C\).](#)

Copies of the full report on Emerging Markets, "The Registration of Pharmaceuticals in Emerging Markets: Submission Strategies and issues of concern in Asia, South America and Central and Eastern Europe", which contains 131 pages, 70 figures and 2 appendices, are available free of charge to CMR International sponsoring companies. The report can be ordered quoting reference number CMR99-108R.

Copies of the full report are also available to sponsoring companies only on the CMR International web site.

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