



R&D Briefing

Reliance on Repetition:

Company Strategies for Use of Foreign Clinical Data

Strategies for the generation of clinical data in different regions

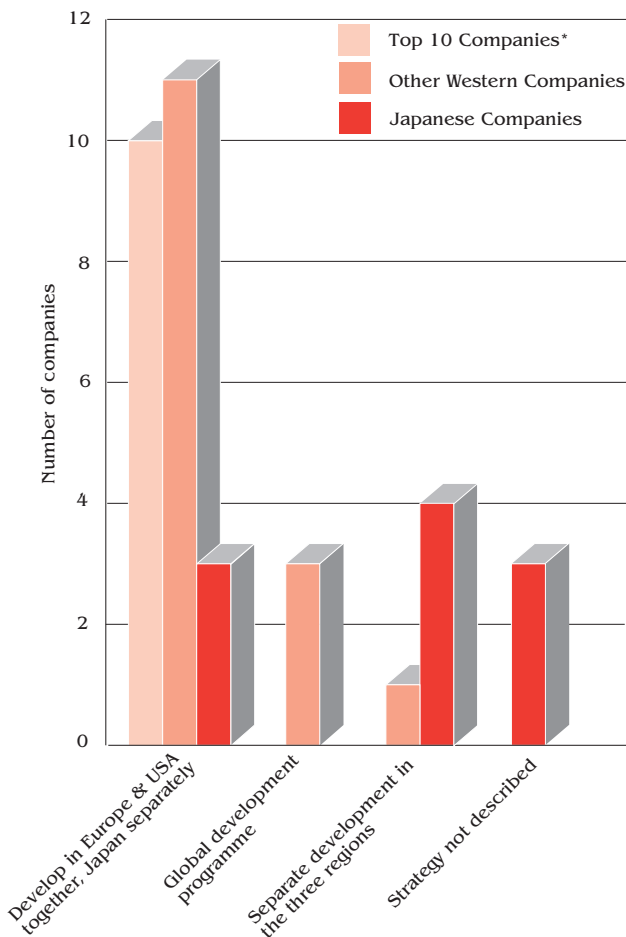


Figure 1: Three general strategies are adopted by companies for generation of clinical data: 24 companies follow a joint clinical development programme in Europe and the USA, whilst generating clinical data in Japan separately; 3 companies adopt a global development programme which involves all three regions and 5 companies develop separately in all three regions.

* Top 10 by pharma R&D spend in 1993 (Scrip 1994).

Clinical trials are time consuming and costly but the data they generate are essential components of any marketing submission for a new product.

When making submissions to regulatory authorities in differing regions of the world, many companies perceive the need for locally generated clinical data. In consequence, investigations are repeated.

To what extent does this happen? Is it necessary? Do regulatory authorities differ in their approach to foreign clinical data? Can repetition be avoided?

These questions underpinned a recent CMR survey into the industry's attitude to the use and acceptance of foreign clinical data in regulatory submissions. The results show that clinical studies are repeated in local populations, due to perceived pharmacogenetic differences, regulatory requirements, or to support pricing or marketing.

This repetition increases both the time and costs of drug development which has considerable implications for the industry as a whole, and is particularly relevant to the ICH (International Conference on Harmonisation) process.

Perspective

Many pharmaceutical research companies see lack of acceptance of foreign clinical data as a major problem in international drug development. Undoubtedly there are still requirements for certain studies to be conducted in local populations. But the attitude of regulatory authorities is evolving and the prospect of harmonisation is under discussion. It is of importance, therefore, to gain insight into current thinking within the industry.

A questionnaire based survey of international pharmaceutical companies was conducted to obtain up-to-date information on:

- generation of clinical data in three regions, Europe, the USA and Japan,
- strategies for submission of foreign clinical data for marketing authorisation.

Thirty-five companies (17 European, 8 American and 10 Japanese) participated in the study. This represents 66% of the companies contacted initially and includes all Top 10 companies by pharmaceutical R&D spend in 1993 (see Table 1).

Table 1
Top 10 Companies by Pharma R&D Spend in 1993

Bayer
Bristol-Myers Squibb
Glaxo
Hoechst
Lilly
Merck Sharp & Dohme
Pfizer
Roche
Sandoz
SmithKline Beecham

(Scrip's 1994 Pharmaceutical Company League Tables, October 1994. Richmond: PJB Publications)

Worldwide or Regional?

Three distinct strategies are adopted for the generation of clinical data (see Figure 1). By far the most popular is joint development in Europe and the USA, with a separate development programme in Japan (24 companies).

In contrast, a smaller group of five companies (four of which are Japanese) favour using separate programmes for clinical research in each of the three regions.

Only three companies aim to follow a truly worldwide development programme, generating clinical data in all three regions simultaneously. From the survey results, other companies appear to be working towards this aim.

Where is the Data Used?

Whereas clinical development strategies may differ, there are strong similarities in the way companies use foreign data. The majority of companies treat all Western data in the same way, whether it is generated in the USA or Europe.

Thus all companies have a strategy for using Phase II and III European data as evidence of safety and efficacy in submissions to the US Food and Drug Administration (FDA). The same is true in reverse for US data, as shown in Figure 2.

There is a perception, often based on experience, that Western data is not acceptable as pivotal to the Ministry of Health and Welfare (MHW) in Japan. This explains why, in submissions to the MHW, Western data is generally supplementary to other data submitted. As such, the aim most often is to support safety and efficacy claims rather than to provide safety evidence alone.

The situation regarding data from Japanese clinical trials is somewhat different. Based on the practices of respondents to the questionnaire, Japanese data does not form an important part of dossiers submitted to Western authorities. Most often it is submitted to both the FDA and European regulatory authorities, on a supplementary basis, for safety purposes only. Exceptions to this generalisation are Japanese companies; almost half aim to use Japanese data to support safety and efficacy claims in Western submissions.

"The mutual acceptance of foreign data would reduce the time and resources required to develop a new medicine for the international market, by eliminating the need for the routine repetition of clinical studies in local populations."

Schematic overview of companies' general strategies for the submission of foreign clinical data

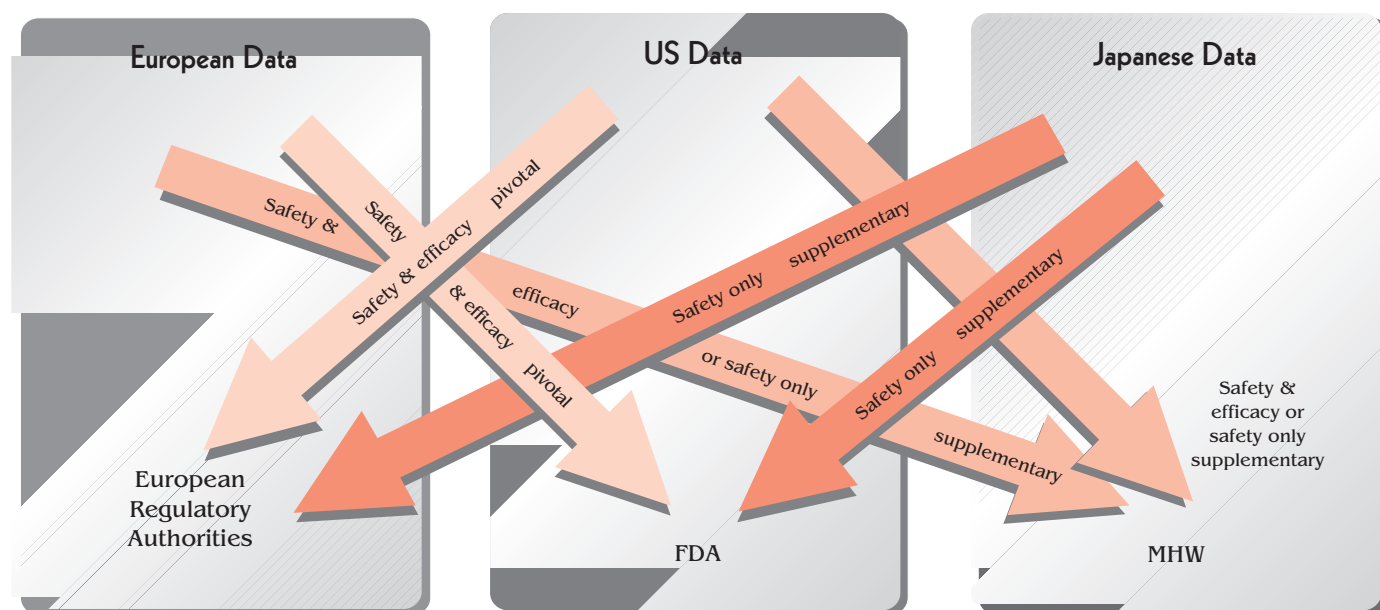


Figure 2: The diagram shows the general strategies of companies for the submission of foreign clinical data to regulatory authorities.

For example, most companies submit clinical data generated in Europe to the FDA as pivotal evidence of a compound's safety and efficacy.

It is interesting to note that 24 companies treat Europe and the USA as one region when generating clinical data.

Past Experiences

Although there is no formal barrier to gaining marketing approval for a new product based on foreign clinical data alone, experience is limited. Since 1986, only three of the companies participating in the survey had been granted approval on this basis in one of the three regions. All were European. A total of four compounds were approved; three involved applications to the FDA and one to European authorities.

Repetition - Route to Approval

In the knowledge that repetition of clinical studies in local markets occurs prior to registration, companies were asked to identify the underlying reasons for this practice. The relative importance of the four main reasons varies according to the phase of the studies (see Figure 3). Thus, in Phase I, pharmacogenetic and regulatory reasons predominate. This response is to be expected as it is a regulatory requirement in Japan for these studies to be repeated for pharmacogenetic reasons.

Once the compound is being tested in patients (Phases II and III) differences in medical practice between the regions emerges as a major reason for the repetition of trials. In addition, by the time a compound has reached Phase III, the pressures of pricing controls and marketing considerations add further weight to arguments in favour of repetition.

In Europe and Japan it is usual to demonstrate efficacy of a new compound using comparator controlled studies. By contrast the FDA require placebo controlled trials. Furthermore, the current requirement in Europe and Japan is for controlled trials to be conducted against the locally preferred medicine as comparator. These are additional factors that have important influences on the repetition of studies in multi-national development programmes.



Reasons for repetition of clinical studies in different regions prior to registration

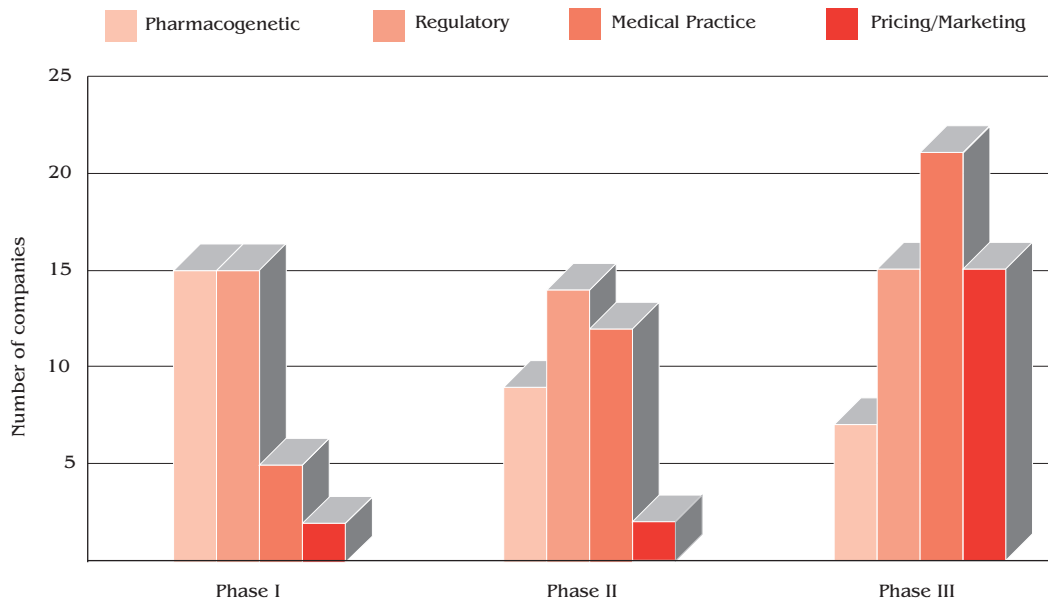


Figure 3: Companies repeat clinical studies in all regions of submission. The major reasons for this include to comply with local regulatory requirements, perceived differences in pharmacogenetics between populations (Phase I) and differences in medical practice (Phase III).

Implications for the Industry

Although there are circumstances where the influence of ethnic factors might justify clinical evaluation in a local population, the routine repetition of studies undoubtedly increases the time and cost of clinical development. One practical way to overcome this unnecessary waste of resources is the introduction of mutual acceptance of foreign clinical data by regulatory authorities. Steps in this direction are being made as part of the ICH E5 initiative.

The main reasons why clinical studies are repeated, according to this survey, are variations in medical

practice around the world and differences in regulatory requirements, often based on pharmacogenetic arguments or differing clinical research methodology. Harmonisation of regulations governing the acceptability of foreign data would therefore be of considerable value to the pharmaceutical industry, by reducing the number of clinical studies that are required for international registration. This in turn would decrease both the time and resources needed to bring an important new medicine to the market. The net effect of this change in clinical strategies is that novel medicines could reach the major markets more quickly, thus ultimately being of benefit to patients waiting for new treatments.

Copies of the full report, "The Use and Acceptance of Foreign Clinical Data: An Industry Viewpoint" which contains 80 pages, 37 figures and tables and 3 appendices, can be obtained at a cost per copy of:

Non-sponsoring organisation	£500
Sponsoring pharmaceutical companies	FREE

These can be ordered, quoting reference number CMR96-17R from Shaïda Dorabjee, Research Services Manager, at the Centre for Medicines Research.

(All cheques should be made payable to Centre for Medicines Research. Non-UK cheques should be in sterling and drawn on a London bank.)



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