



R&D Briefing

Heading for Harmonisation

Impact of ICH Efficacy Guidelines

Company strategies for the implementation of finalised ICH efficacy guidelines

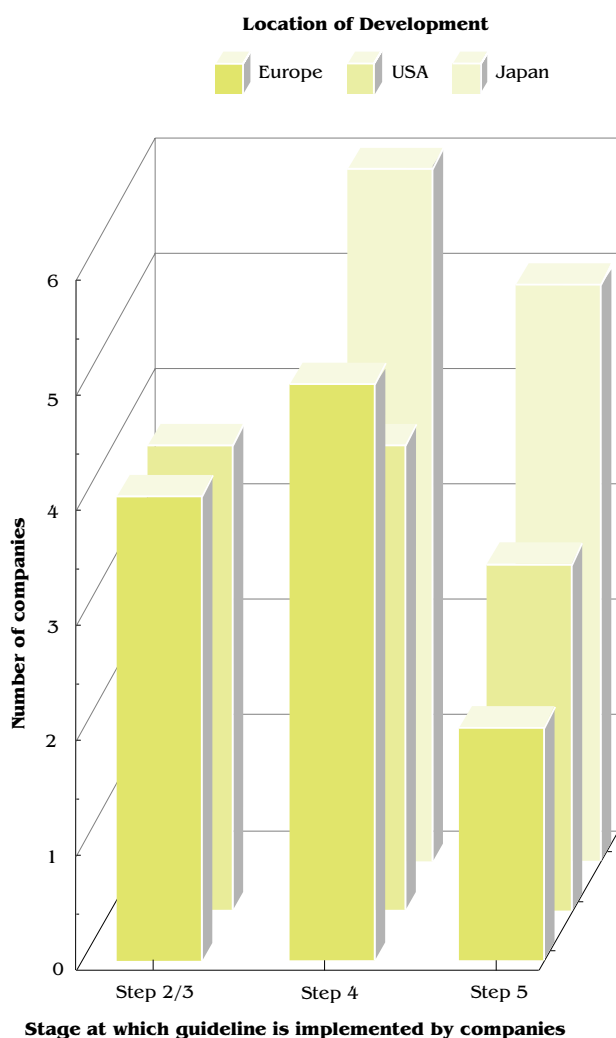


Figure 1 For development conducted in Europe or the USA, guidelines are implemented at an earlier stage (usually Step 2 or Step 4) than in Japan (at least Step 4 and often Step 5).

Investment in the International Conference on Harmonisation (ICH) in terms of time and resources has been considerable. In addition, achievement of the underlying ICH objective, greater harmonisation of regulatory requirements for pharmaceutical compound registration, will have a marked effect on industry practices.

What is the impact of ICH efficacy guidelines on global clinical development strategies for new medicines?

At what stage are guidelines adopted and are difficulties experienced when implementing them?

What is the perceived effect of the efficacy guidelines on costs, patient numbers, quality and clinical development time?

To determine the opinions of the industry on these issues, CMR International gathered information from European, Japanese and US based pharmaceutical companies and found that, in general, the finalised efficacy guidelines have been of benefit, and have increased the efficiency of companies' global clinical development programmes.

Finalised ICH efficacy guidelines

Number	Topic	Step 4 Date
E1A	The extent of population exposure required to access clinical safety	October 1994
E2A	Clinical safety data management	October 1994
E3	Clinical study reports: structure and content	November 1995
E4	Dose response information to support drug registration	March 1994
E6	GCP consolidated guideline	May 1996
E7	Studies in special populations: geriatrics	June 1995

Perspective

In order to ascertain company strategies for adoption of ICH efficacy guidelines, and opinions on the impact of these guidelines on global clinical development, CMR International conducted a study amongst leading European, Japanese and US based pharmaceutical companies and found that, the finalised ICH efficacy guidelines have been of benefit, and have increased efficiency within the global clinical development programmes of the respondents.

At the time of this questionnaire-based survey, six efficacy guidelines from the International Conference on Harmonisation (ICH) were finalised, having been adopted at Step 4 (Table). The study assessed the impact of these guidelines on clinical research programmes, in terms of strategy and performance of major pharmaceutical companies, and sought to identify any difficulties in guideline implementation. In addition, this study sought to canvass the industry on the future of ICH.

Implementation Strategy

The 16 major pharmaceutical companies participating in this survey (5 European, 4 Japanese and 7 US based) had considerable experience of taking compounds through clinical development using the guidelines, the mean number of compounds per company ranging from five to 11, for any one guideline. A majority of the respondent companies employ a strategy for implementing guidelines, with the stage at which the guideline is adopted varying according to the region of pharmaceutical development (Figure 1). Finalised guidelines are implemented as a matter of policy by 13 companies, usually through incorporation into SOPs which are applied on an international scale.

Overall, implementing ICH efficacy guidelines has generated relatively few problems, either within the company or when making submissions to regulatory authorities (Figure 2).

Implementing finalised ICH efficacy guidelines; were problems experienced?

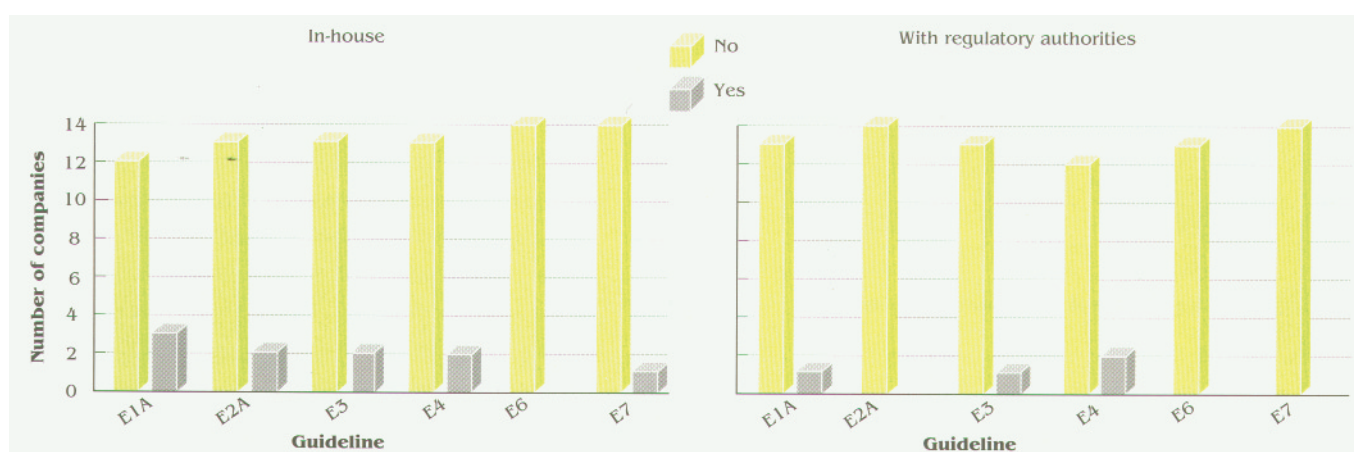


Figure 2 Overall, few companies have experienced problems, either in-house or with regulatory authorities, when implementing finalised ICH guidelines.

Quality of the efficacy assessment: Impact of finalised ICH efficacy guidelines

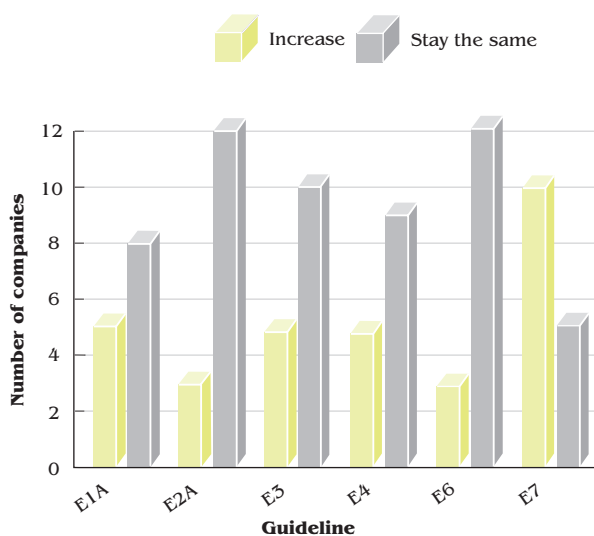


Figure 3 Responses to the question, “What has been the impact of this guideline on the quality of efficacy assessment (or what will be the impact if it has not yet been implemented)?”, were divided between quality increasing or staying the same. The guideline that has been implemented for the longest amount of time, E7, seems to have had the most positive impact on the efficacy assessment.

Impact on Clinical Development

Population size

Only two of the guidelines have had a noticeable effect on the numbers of patients recruited into clinical trials. As a consequence of E7 (studies in special populations: geriatrics) almost half the companies have increased patient numbers, which is to be expected, as the inclusion of a larger proportion of elderly patients in clinical trials is encouraged by this guideline.

The population exposure guideline (E1A) has had a varied impact, with approximately equal numbers of companies reporting increases, no change or decreases in patient numbers included in their trials. This is perhaps a more surprising finding, as it was envisaged that patient numbers would fall following adoption of this guideline. However, as with any change in the regulations governing clinical development, the impact will vary according to the pre-existing development strategy of individual companies.

Development time and costs

Overall, the guidelines have made little impression on either total drug development time or individual study

time. Again, the exceptions to this are E1A and E7. Those companies that have seen reductions in the numbers of patients recruited in clinical trials in many cases also experienced shorter study times, whilst companies that increased patient recruitment were likely to see associated increases in either study time, or total development time.

All the guidelines have had some impact on resources. Between three and eight companies, for any one guideline, have experienced increased financial costs and for nearly all companies manpower requirements have either increased or remained unchanged. However, the eventual expectation of many respondents was that the increased standardisation, harmonisation and acceptance of foreign data facilitated by these guidelines would ultimately reduce the overall cost of clinical development.

Quality

The guidelines are having a positive effect on the quality of clinical research; the greatest positive impact on the quality of the efficacy assessment is seen with guideline E7, which has been implemented the longest (*Figure 3*).

Conduct and strategy

Implementation of three of the guidelines (E1A, E2A and E7) has already altered the conduct of clinical trials for the majority of companies. In addition, over half of the respondents envisage company strategy for the conduct of trials or submission of results changing in the future as a consequence of the E1A guideline. This is to be expected, as advice on submission strategies for Phase III study data is contained within this guideline.

Foreign data

In general, respondents indicated that the harmonisation of efficacy guidelines is expediting the development of a globalised clinical package within their company, and is increasing the acceptance of foreign clinical data.

At the time of this survey, guideline E5 on ethnic factors in the acceptability of foreign clinical data had not yet reached Step 2. As this guideline is expected to have a major impact on global clinical development, respondents were asked how they believed this guideline would affect their strategy. The majority (13) indicated that, once finalised, this guideline will at least partly address current problems in this area, and will contribute significantly to increased acceptance of foreign clinical data. The concept of bridging studies is considered to be a viable one, provided that industry and regulatory

Benefit of ICH efficacy guidelines

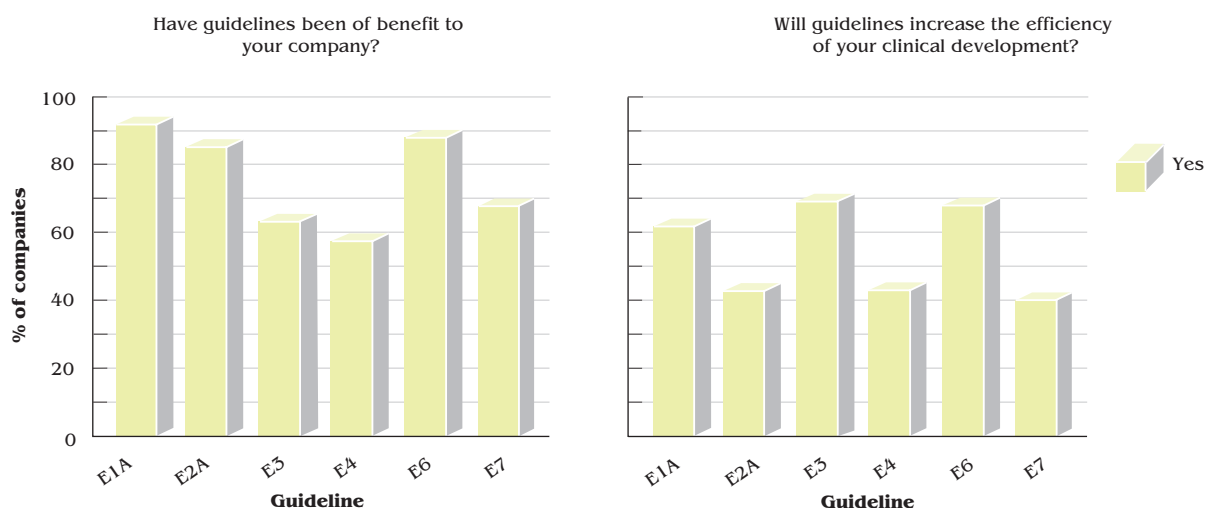


Figure 4 Although there have been mixed opinions on the tangible benefits of the ICH efficacy guidelines in terms of time, costs and patient numbers, the majority of companies believe that the guidelines have been of benefit to them, and will increase the efficiency of their clinical development programmes.

authorities work together more closely during the development of the clinical programme.

Benefits for Companies

In spite of the lack of immediate savings in time and resources, most companies believe that the guidelines are having a positive effect on the efficiency of their clinical development programme. In addition, increased efficiency in clinical development is anticipated by 40% of respondents for all guidelines, and over 60% of respondents as a result of E1, E3 (Clinical study reports) and E6 (Good Clinical Practice) (Figure 4).

There is considerable support for the ICH process, and most companies cited positive outcomes, including

harmonisation and clarification of requirements and the increased acceptance of foreign clinical data. In addition, the majority of companies believe that ICH has made a significant contribution to the eventual aim of a global clinical dossier.

The Future of ICH

Overall, the perception of the ICH process by major pharmaceutical companies was positive, with 15 companies indicating that the initiative should continue in the future. Six companies believe it should continue unchanged beyond ICH 4, while nine would prefer a modified format.

Copies of the full report, "The Impact of ICH Efficacy Guidelines on the Clinical Development of Medicines" which contains 64 pages, 18 figures and tables, and 4 appendices, can be obtained at a cost per copy of:

Non-sponsoring organisations	£500
Sponsoring pharmaceutical companies	FREE

These can be ordered, quoting reference number CMR97-57R, from Shaïda Dorabjee, Research Services Manager, at Centre for Medicines Research International.

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

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