



# R&D Briefing

## Perfecting a Procedure

### Evolution of mutual recognition during the transition period

Selection of Reference Member State

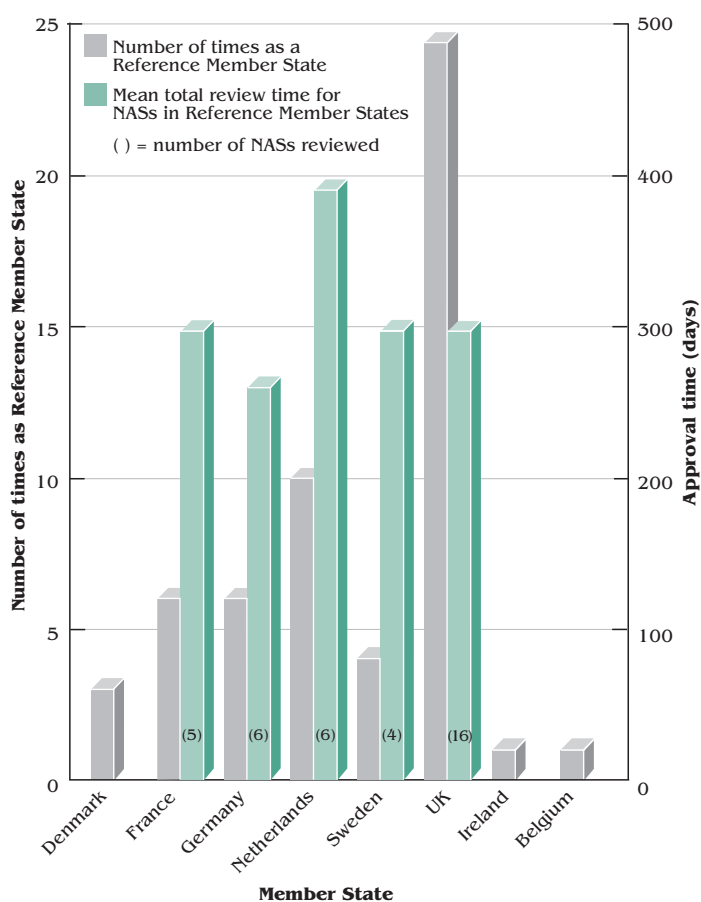


Figure 1 For the 55 new applications submitted to the mutual recognition procedure, 8 different Member State authorities have acted as the Reference Member State. Five countries have acted as the Reference Member State for the 37 new active substances (NASs): France, Germany, The Netherlands, Sweden and the UK. Sweden was the quickest, on average, to grant the initial marketing authorisation for the 37 NASs in this cohort.

- The beginning of 1998 marked the end of a three-year transition period for the new medicines authorisation procedures in Europe. The choice for industry now lies solely between the centralised and mutual recognition procedures; multiple national applications are no longer an option.
- Various initiatives have been introduced to overcome initial concerns with the mutual recognition procedure. Are these concerns being adequately addressed? Will the new initiatives produce a transparent, well defined process that can be benchmarked and thereby improved? Are further actions required before the process of mutual recognition can operate smoothly?
- With data from 55 new applications submitted to mutual recognition, the final report on a CMR International survey reveals both the successes and difficulties that have been encountered during the transition period. It identifies issues still to be addressed by industry and regulators to ensure successful mutual recognition in 1998 and beyond.

## Perspective

The three-year transition period for the introduction of the centralised and mutual recognition procedures for obtaining a marketing authorisation for medicinal products in the European Union (EU) ended at the beginning of 1998. It is now possible to review the evolution of mutual recognition and determine whether it has reached the level of efficiency already enjoyed by the centralised procedure.

This final update from a prospective survey, initiated in 1995 by CMR International, provides information on 55 new applications through the mutual recognition procedure made by 30 companies (see also *R&D Briefing No 9; Industry Insights*) during the transition period. Line extensions were the reason for 18 of these applications while the remainder related to new active substances (NASs).

## Exercising Choice

Not all countries were selected by sponsoring companies to act as the Reference Member State; the

UK has been the most common choice followed by The Netherlands (*Figure 1*). Reasons for the selection included previous experience and/or good relations with the agency, size of the market for the product or language considerations. For the 37 NASs on average, Sweden was the quickest to grant the initial marketing authorisation in instances where it was the Reference Member State.

For the vast majority of compounds, mutual recognition was sought in 12 or more Member States; Italy, Spain and Portugal were the concerned Member State most often. Each EU member acted as a concerned Member State between 12 and 53 times.

## Procedural Targets

The Best Practice Guide for Member States, introduced in October 1996, proposed a number of targets. That of 10 working days for confirmation of a valid application has not been achieved routinely by any concerned Member State, although the times taken show less variability than before the Best Practice Guide was issued.

Relationship between time from mutual recognition start to national licence

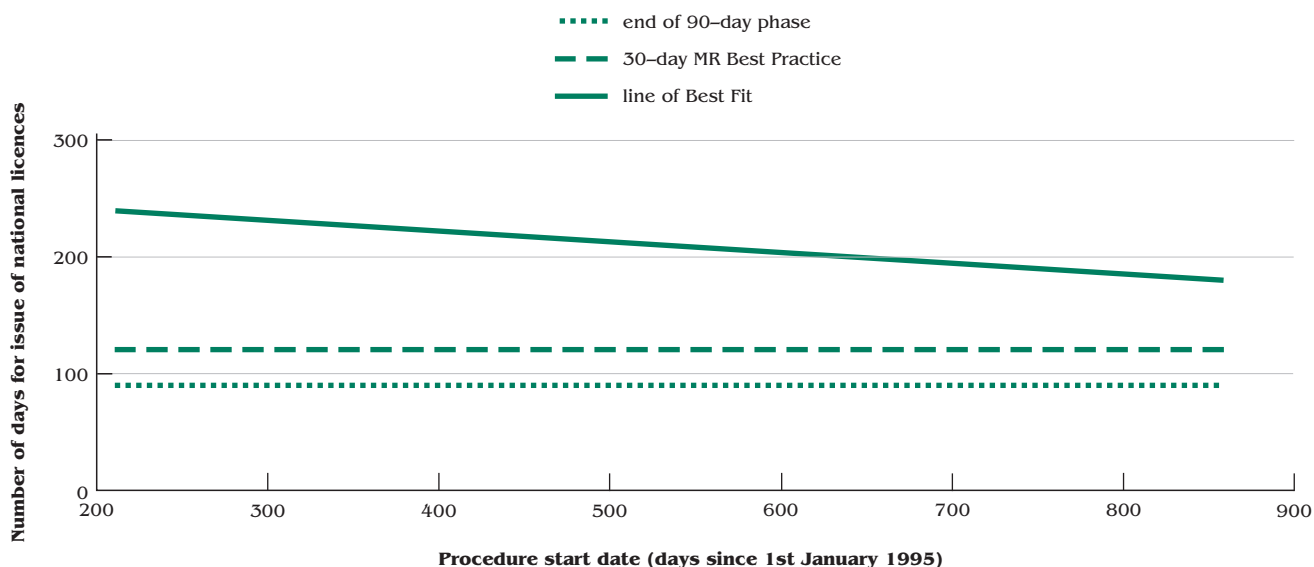


Figure 2 A linear regression line shows the relationship between the time from the start of the 90-day clarification and discussion phase of the mutual recognition procedure to the issuance of national licences for each country and each compound, against the time since the instigation of mutual recognition in January 1995. Since the beginning of the mutual recognition procedure the time taken to issue national licences has shown a steady decrease although 'Best Practice' has not yet been achieved.

Once the 90-day clarification and discussion phase of mutual recognition is complete, national marketing authorisations should be issued within 30 days. This Best Practice target has yet to be achieved routinely. However, since the inception of the mutual recognition procedure there has been a steady improvement in the average time taken (Figure 2). Overall, Denmark and the UK have been the quickest to grant national licences.

## En Route to Mutual Recognition

For each application, concerned Member States have 90 days in which to identify and address potentially serious public health concerns. Although most questions were forwarded by the Reference Member State between days 50 and 65, some issues were raised much later.

The majority of questions concerned Parts I and II of the dossier, with an average of 35 questions per compound in Part I, and 18 in Part II. Importantly, few of these were considered by companies to be critical to eventual mutual recognition (*that is, likely to lead to*

*arbitration unless satisfactorily answered*) as illustrated for a group of 23 compounds (Figure 3). Overall, Germany generated the most queries but, for Part I, Sweden, The Netherlands and the UK had similar levels of questioning.

## Reaching the Goal

In this survey, 48 compounds completed the clarification and discussion phase but a relatively high number of withdrawals (relating to 27 compounds) from one or more concerned Member States occurred in the process (Figure 4). Companies generally chose withdrawal to avoid arbitration or compromising the harmonised Summary of Product Characteristics.

Increasing numbers of arbitrations and withdrawals are likely unless the “break-out” sessions of the mutual recognition facilitation group reach their full potential. Over half the companies expressed dissatisfaction with the session at which their product was discussed, often due to the absence of appropriate representatives from each of the relevant concerned Member States.

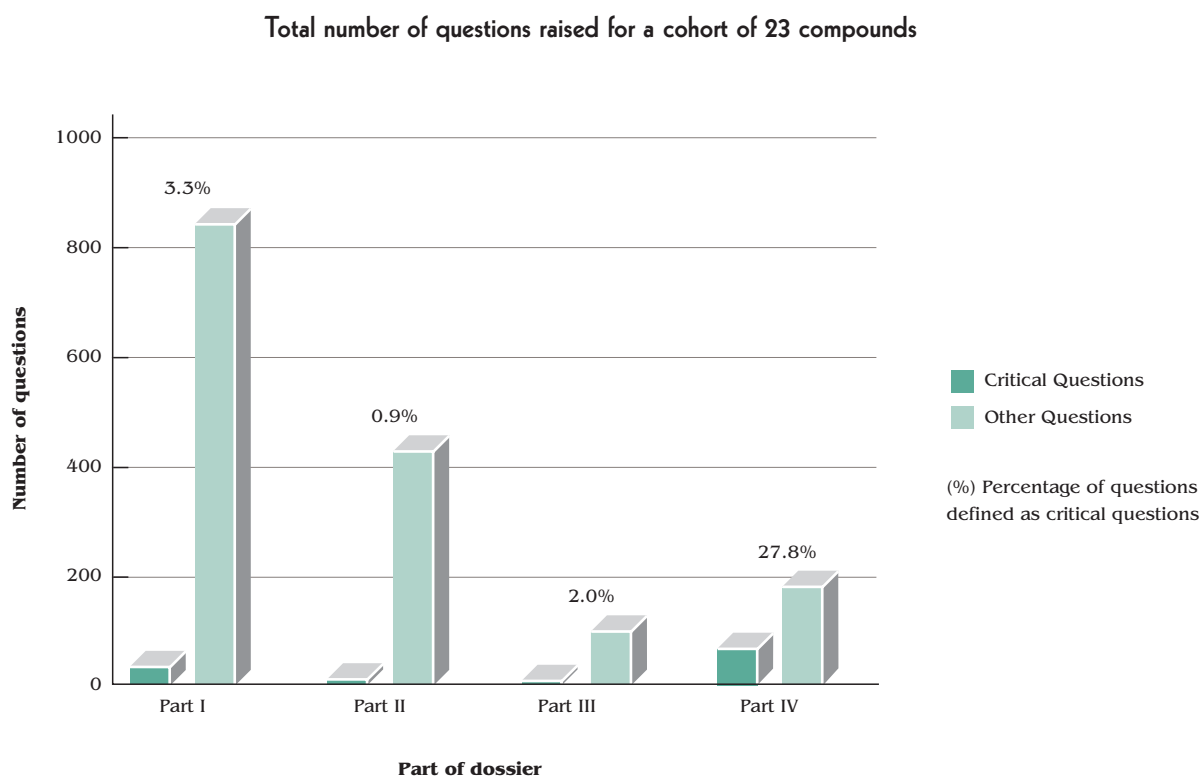


Figure 3 For a cohort of 23 compounds the majority of questions asked during the 90-day clarification and discussion phase concerned Parts I and II of the dossier. For Part IV of the dossier, approximately 28% of the questions asked were considered critical whilst only 6% of the questions on Parts I, II and III were considered by the company to be likely to result in arbitration if not satisfactorily answered.

## Withdrawals of applications from concerned Member States during mutual recognition

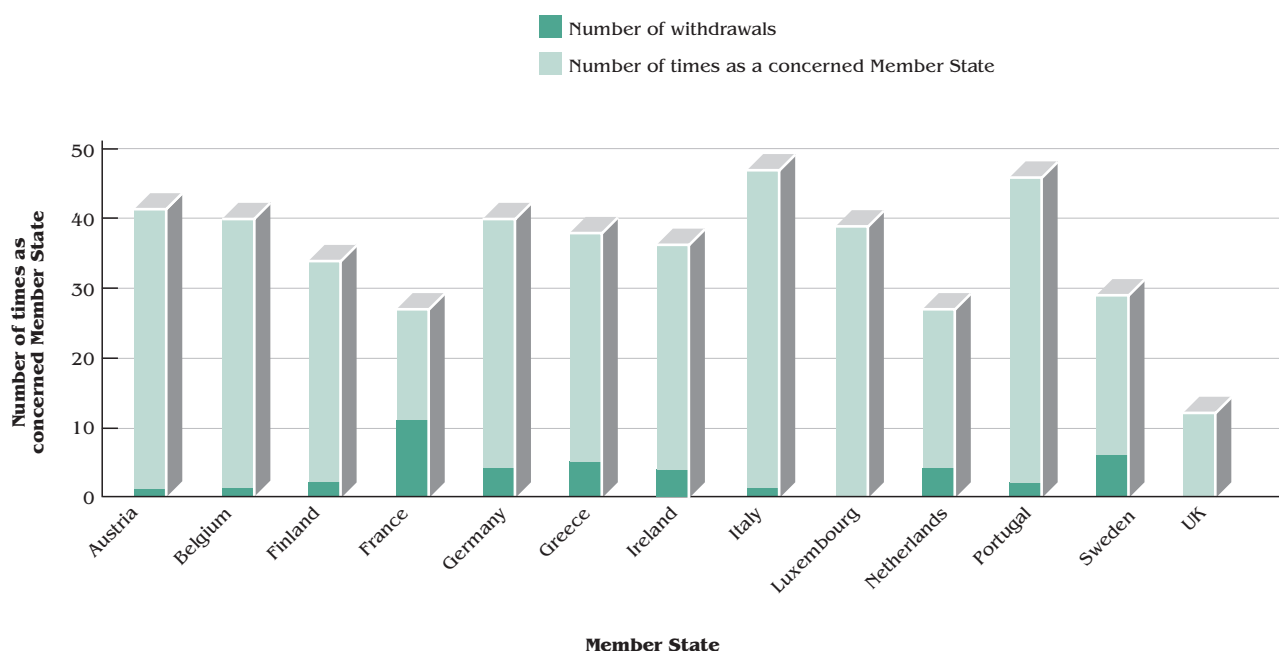


Figure 4 Member States had acted as concerned Member States between 12 and 47 times for the 48 compounds that had completed the 90-day clarification and discussion phase. Twenty-seven of these compounds were withdrawn from one or more concerned Member States during this phase, with France being the most common concerned Member State in which withdrawals occurred (11 times).

monitor the timing of mutual recognition applications. This initiative is welcomed and once operational it will increase transparency, encourage authorities to improve performance and assist companies in making informed decisions regarding their regulatory strategy in the single community system.

### Towards Transparency

Input from industry and reviewers remains essential, so that mutual recognition offers a viable alternative to the centralised procedure for the licensing of medicinal products in the EU. A recent joint initiative by the European Commission and Member State authorities has resulted in the EudraTrack system which will

With publicly available information currently lacking, this survey provided a valuable insight into the performance of the mutual recognition procedure during the transition period. Not only were issues of concern identified but also the achievements to date and the hurdles yet to be overcome, if mutual recognition is to evolve into an efficient and transparent review system.

A copy of this R&D Briefing is available on the CMR International web site. Additional paper copies can be obtained free of charge from the Centre.

Copies of the full report, "Performance of the European Mutual Recognition Procedure: Submissions in the Transition Period January 1995 – November 1997", which contains 68 pages, are available **free of charge to CMR International Sponsoring Companies, and at a cost of £500 to other organisations**. The report can be ordered quoting reference number CMR98-61R2; cheques should be payable to **CMR International** and non-UK cheques should be in sterling and drawn on a London bank.

Copies of the full report are also available in electronic format for Sponsoring Companies. For further details please contact Shaida Dorabjee, Research Services Manager, CMR International.

July 1998

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