



# R&D Briefing

## Profile of Performance (2)

### Similarities and Differences in Regulatory Approval Times

Median NME approval times in major markets 1995-1997

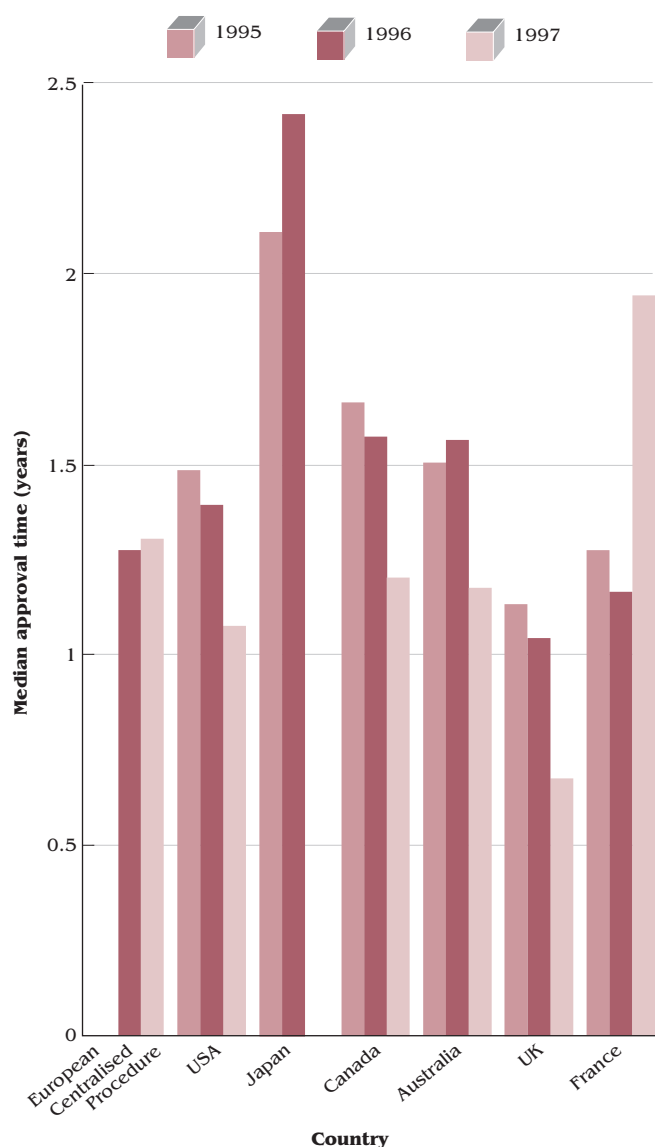


Figure 1 This analysis excludes compounds approved in Europe under the Mutual Recognition procedure, unless the authority under study was the Reference Member State.

- In the fast changing world of pharmaceuticals, companies are continuously wishing to reduce development times. One component remains outside their direct control - that of the regulatory review process. As a consequence, approval times for potential products are under constant scrutiny, both by an industry needing to forward plan and by regulatory agencies seeking greater efficiency.
- The early to mid 1990s showed marked reductions in regulatory review times as performance improvement initiatives were implemented. Have these levels been sustained or are approval times continuing to decrease? Is there uniformity throughout the EU following implementation of the Centralised and Mutual Recognition procedures? Where are the similarities and differences around the world?
- As part of its ongoing programme to monitor regulatory performance, CMR International has analysed trends between 1995 and 1997. Review times continue to decrease, allowing patients earlier access to important new medicines.

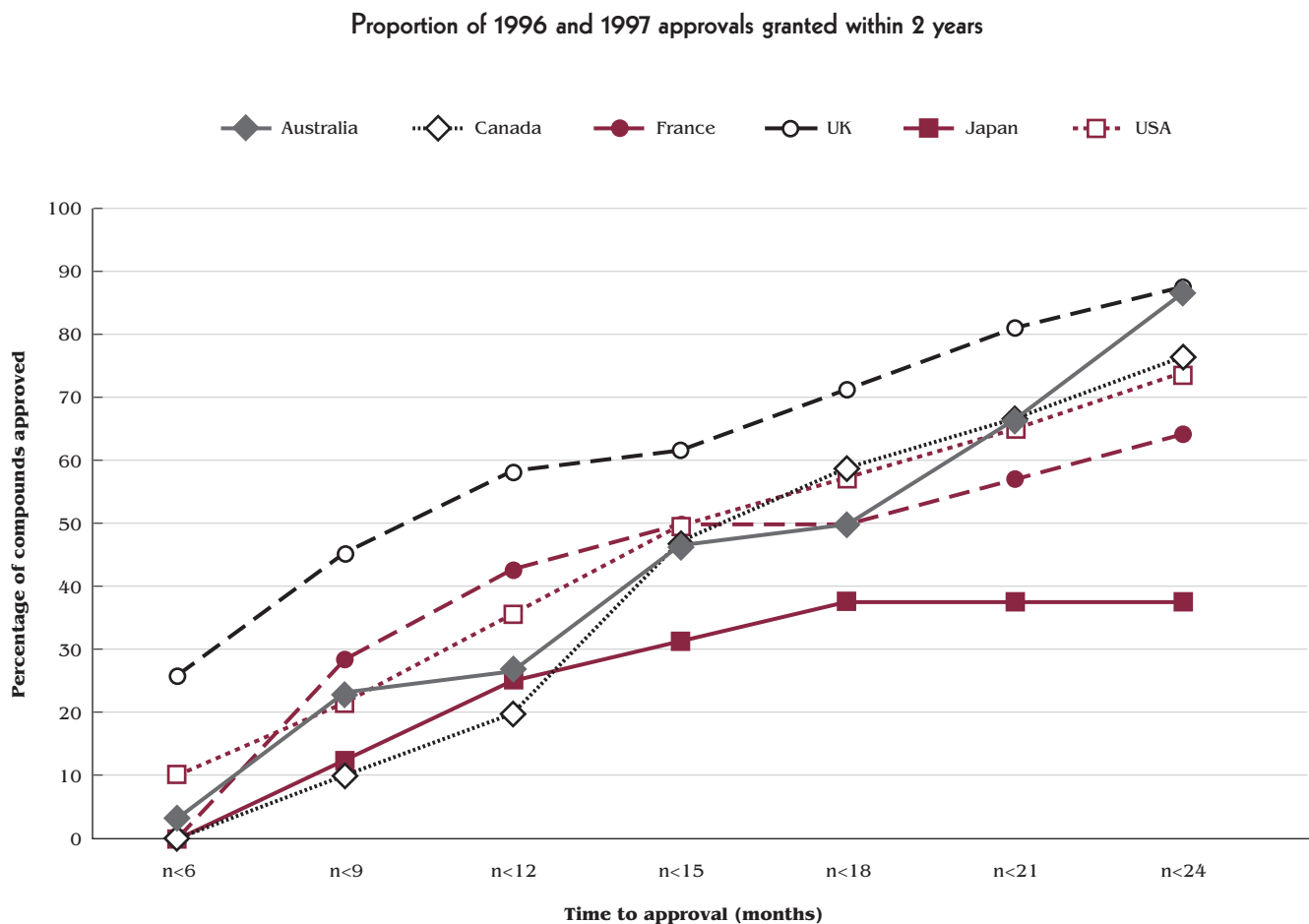
## Perspective

An insight into regulatory processes around the world between 1990 and 1995 was provided in a previous R&D Briefing, No. 10, (*Profile of performance; Trends in approval times during the 1990s*). This showed not only that the time taken from submission of a dossier to marketing approval was decreasing, but also that differences between national regulatory agencies in approval times were diminishing.

The pressure on regulatory authorities to cut review times has continued throughout the decade. Well documented performance improvement initiatives, such as the Prescription Drug User Fee Act in the United States, the Evans & Cunliffe report in the United Kingdom and the Baume report in Australia have all had an impact. In addition, the introduction of the

Centralised and Mutual Recognition procedures in 1995 for the European Union (EU) has dramatically altered the European regulatory environment.

It is important for companies to keep abreast of these changes which, though beyond their direct control, are essential for accurate forecasting within the drug development process. To this end, CMR International maintains an ongoing programme for routinely collecting data on approval times from pharmaceutical companies and regulatory authorities worldwide. This annual activity is augmented by information from the public domain, such as that published by the EMEA (European Agency for the Evaluation of Medicinal Products).



**Figure 2** This analysis excludes compounds approved in Europe under the Centralised procedure, or under the Mutual Recognition procedure, unless the authority under study was the Reference Member State.

## Worldwide Performance

The downward trend in approval times seen in the first half of the decade continued in the period from 1995 to 1997 in most markets (*Figure 1*).

France was a notable exception; the apparent increase in median approval time for 1997 was, however, influenced by a number of outliers. France is a frequent choice to act as the Reference Member State within the EU Mutual Recognition procedure; however, under the new procedures the total number of dossiers to be reviewed by any Member State has decreased.

A target average review time of 12 months has been set in Japan, to be achieved by the turn of the century, and changes are already taking place. Information relating to approvals in Japan during 1997 was limited and has therefore been omitted from the graph.

## Estimating Efficiency

The relative efficiency of the different regulatory authorities and the likelihood of a compound being approved within a given time-frame can be estimated from the cumulative percentage of approvals within a fixed period. The UK continues to demonstrate considerable efficiency, with around 60% of those approvals issued in 1996 and 1997 having been granted within 12 months (*Figure 2*).

This analysis highlights the fact that review times of six months or less have been achieved, although some authorities have yet to meet such time lines.

## Uniformity in Europe?

It might be expected that the implementation of Mutual Recognition (MR), with defined timelines, would

European national and Concerned Member States (CMS) approval times (1996 and 1997)

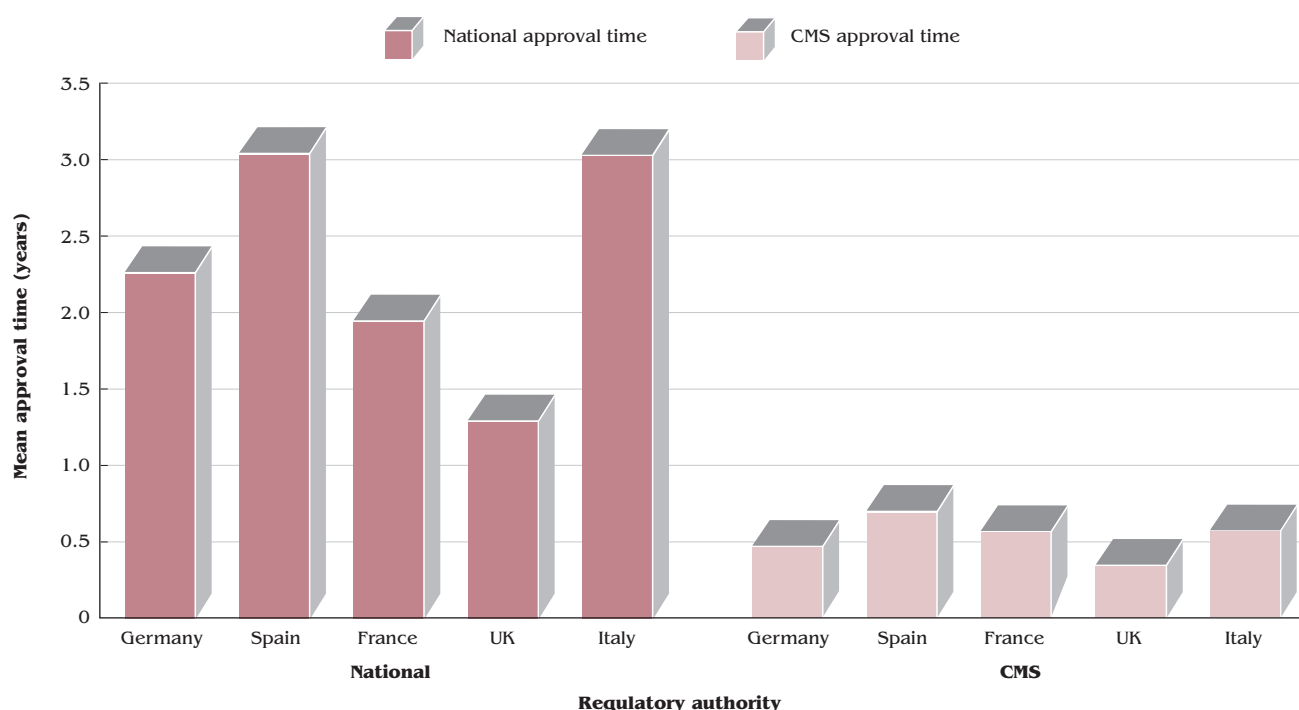


Figure 3 Time 0 represents the submission of a national application (for national approval time) or the start of the 90-day discussion phase of MR (for CMS approval time).

NB. 'National' assessment times are a combination of occasions when the authority has acted as the Reference Member State in a Mutual Recognition procedure, plus any occasion where the authority performed a single national assessment of a new chemical entity.

## Comparison of approval times through Mutual Recognition and the Centralised procedure 1996-1997

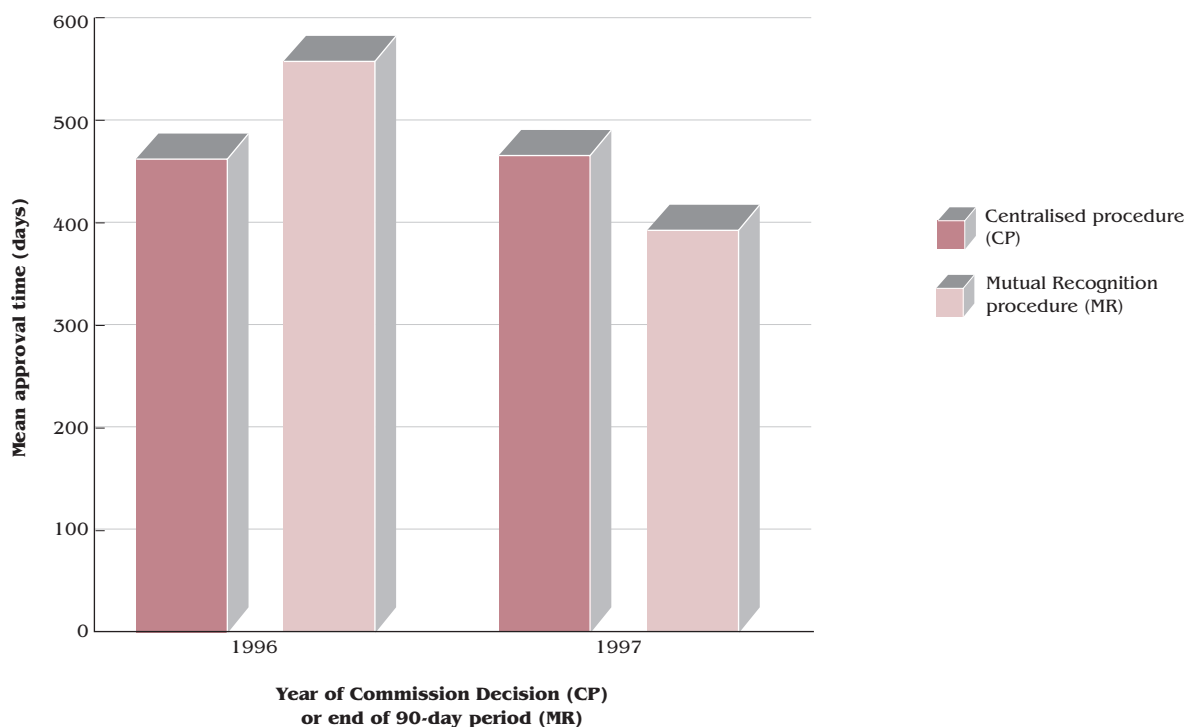


Figure 4 This analysis considers the time from EMEA application date to the Commission's decision date for CP, or date of application to Reference Member State to end of the 90-day clarification/discussion phase for MR.

diminish differences in approval times between Member States when conducting a national review. A comparison of national assessment times for the five largest European markets, however, shows that marked differences remain (Figure 3).

The UK authority has been the quickest to review the dossier and grant marketing approval while acting as the Reference Member State in MR (or undertaking purely national assessments) with a mean approval time of 1.24 years. Likewise the UK authority has been the fastest to mutually recognise approvals granted by other authorities.

By contrast, in Spain and Italy the agencies have, on average, taken more than twice as long as the UK to grant approvals and frequently have failed to meet the best practice deadlines for concerned Member States within the MR procedure.

Despite this, there has been marked improvement in overall performance of Mutual Recognition, with an average reduction in approval time of 167 days between 1996 and 1997. However, within the Centralised procedure (CP) mean approval times have remained essentially unchanged, at over 450 days (Figure 4); this is not surprising in view of the rigid time-frame for the procedure set by the European Commission.

### The Competitive Edge

European approval times must also be competitive on the world stage. However, performance within the Centralised procedure does not compare favourably with that being achieved in the US. This is illustrated by a group of 18 compounds, each the subject of submissions within three months during 1995-1998 to both the US and European agencies. The median approval time was just 0.52 years in the United States whereas the Centralised procedure took 1.08 years.

## Regulatory approval time for compounds submitted to 5 major markets within 6 months (1995-1997)

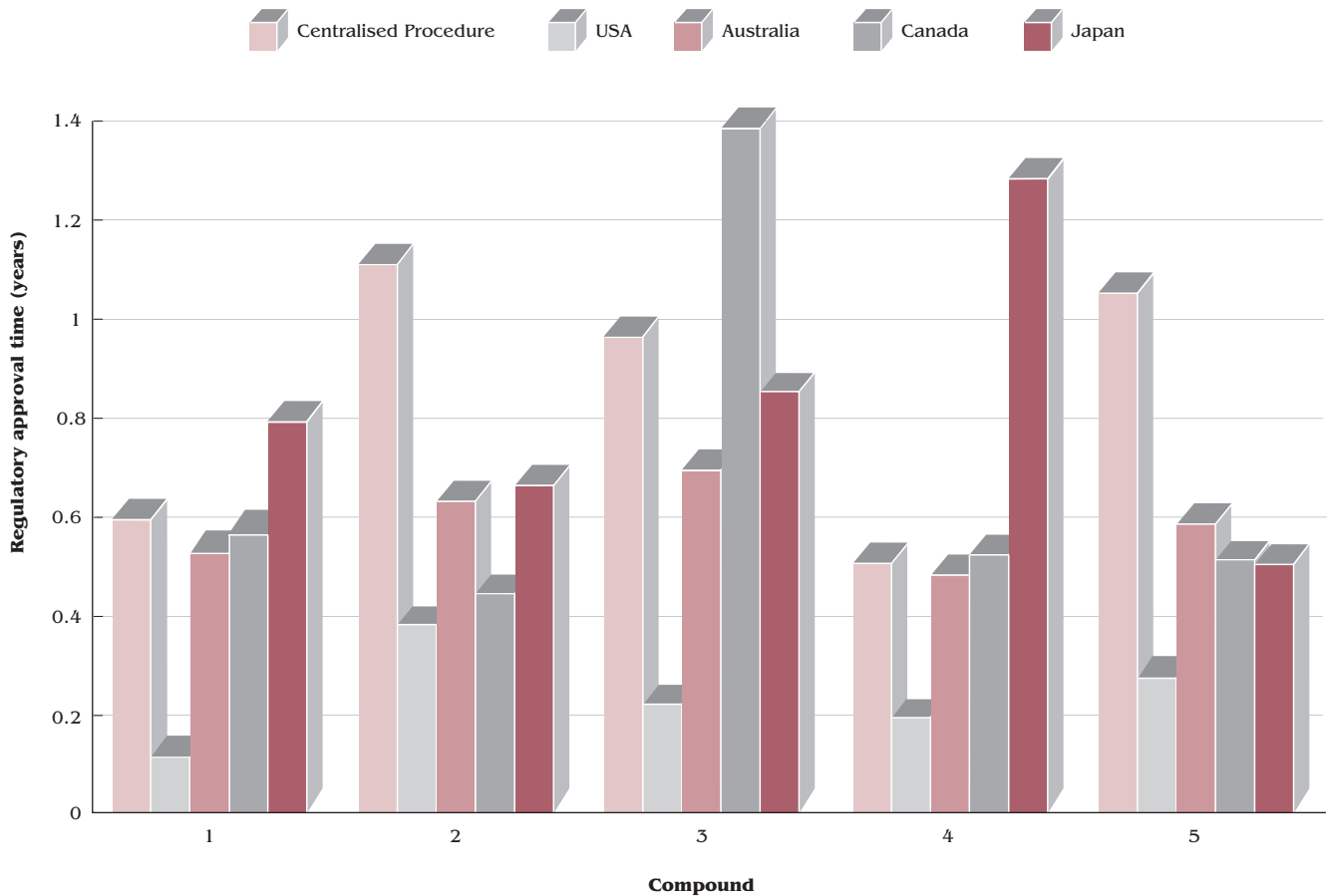


Figure 5 Despite submissions being made within a similar time frame, during which it can be assumed that the dossier is unlikely to change significantly, there were marked differences in approval times for these compounds by the different agencies, even though all 5 compounds were assigned 'priority' status in the USA.

This finding can be partially explained by the level of resources available to the US authorities, coupled with the opportunity for fast track, priority reviews. Even so, it raises the question of whether Europe is denying patients fast access to new medicines by being bound to rigid time lines. After three years in operation, is it time to review targets within the Centralised procedure?

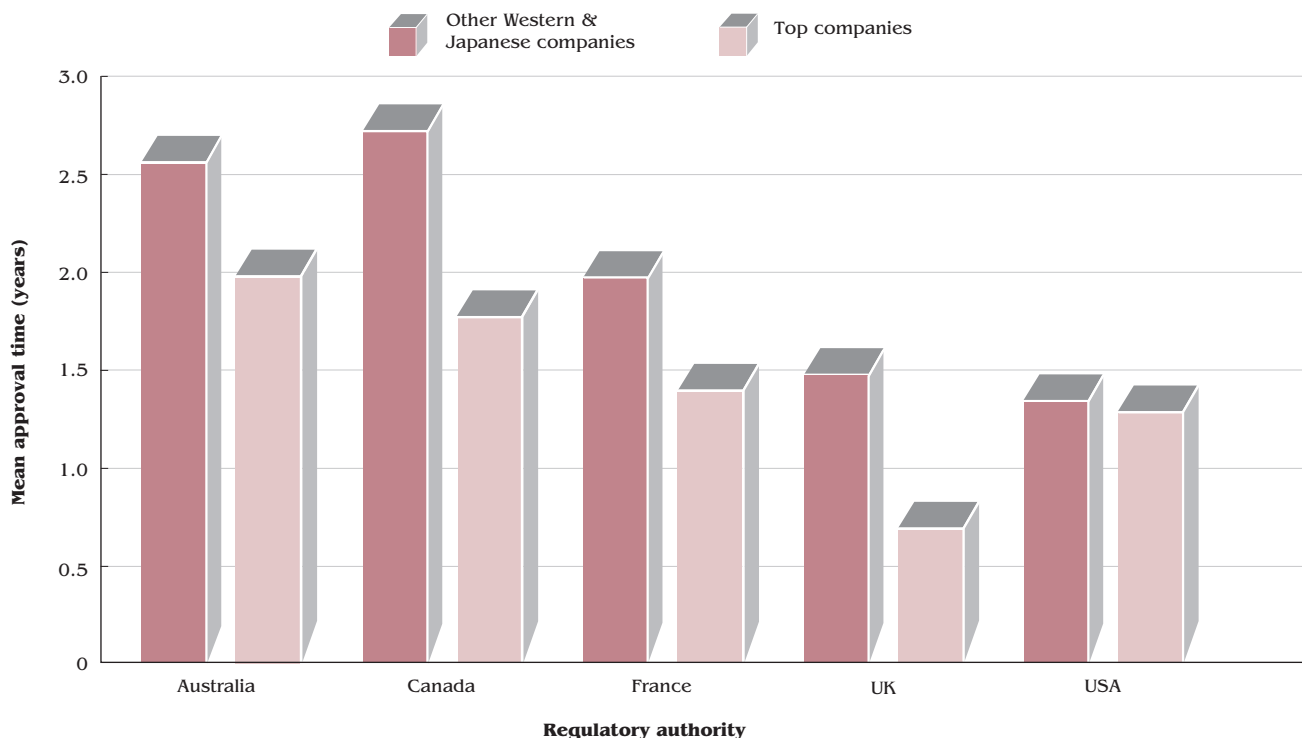
To obtain a broader and more accurate comparison, compounds were identified for which submissions had been made within the same time-frame (six months) to five key authorities. Although these "simultaneous submissions" are the stated objective of a number of companies, only five such compounds were identified. Actual approval times for each compound (Figure 5) emphasise appreciable differences between the authorities; even though all five compounds received

priority review in the US and can therefore be considered to be important therapeutic advances.

### The Bigger the Better?

The wide discrepancy in resources available to authorities will influence regulatory approval times. So too might the experience and size of the company submitting the dossiers. Larger companies are likely to have accrued greater expertise not only in compiling and submitting the dossier to disparate agencies but also in responding promptly to their queries during the review process. This is borne out by the analysis of approvals granted in 1997, divided according to company size (Figure 6).

## Mean approval time for compounds submitted by top 15 companies compared to other Western and Japanese companies 1997



**Figure 6** In 1997, dossiers submitted by companies ranked in the top 15 by pharmaceutical R&D spend were approved substantially more quickly than those submitted by other companies in the authorities studied.

Dossiers submitted by companies ranking within the top 15 by pharmaceutical R&D spend were approved substantially more quickly by four of the five authorities.

### Influencing Factors

In the period 1995 to 1997, regulatory approval times in major world markets continued the downward trend of

previous years. However, marked differences in levels of efficiency and performance between agencies, even those within the EU, remain. Underlying factors influencing overall approval times include the conduct and management of the review process, the implementation of quality control measures and the availability of resources within each agency. Each warrants detailed study to further improve the review process.

A copy of this R&D Briefing is available on the CMR International web site.

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