R&D
BRIEFING
No. 31

PROFILE OF PERFORMANCE (3): REVIEW TIMES – IS THERE STILL ROOM FOR IMPROVEMENT?

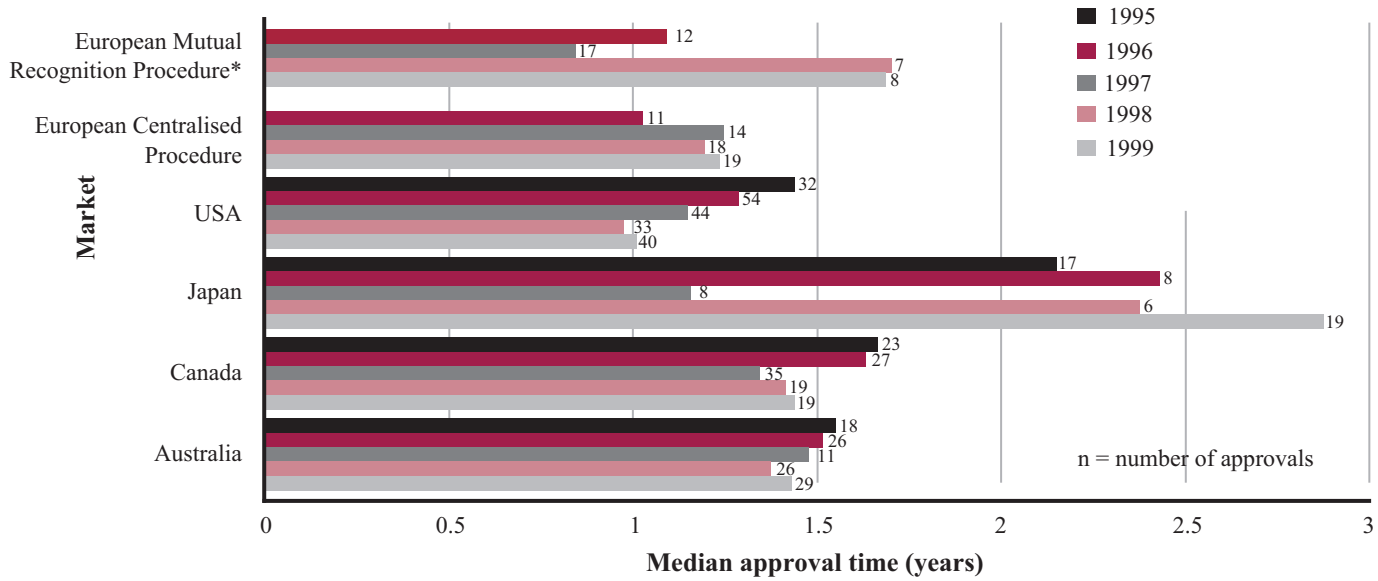
Key Messages

- Performance improvement initiatives established by regulatory authorities in the early 1990s have resulted in the reduction, and in recent years, stabilisation of approval times in several markets.
- The European licensing systems continue to evolve and are currently subject to an operational review. Variations are evident between the two licensing procedures, particularly in terms of overall performance.
- Comparisons of approval times in Europe and the USA are often sought as these allow the investigation of the underlying review processes which is important in terms of patient access to new medicines. There appears to be concordance of overall review time between Europe and the USA, however the majority of dossiers are not submitted simultaneously to both markets.

Perspective

Over the last decade there have been major improvements in the regulatory environment which have shortened the time it takes to bring new drugs to market. The introduction of performance improvement initiatives, targets and user fees in the early 1990s have facilitated more efficient review practice within defined timelines. Companies also have a considerable interest in the predictability, quality and timeliness of the regulatory review procedure.

Figure 1 *Median approval times in major markets 1995-1999*



Approval times for the centralised procedure are taken from the EMEA application date to the Commission's decision date; for MR*, from the date of application to RMS to the end of the 90-day discussion phase. The data-set represents an overall average of approximately 75% of all NAS approvals in these markets between 1995 and 1999.

The general downwards trend in review times seen in most markets between 1995 and 1997 appears to have stabilised over the last two years (Figure 1). However, the USA appears to be an exception having achieved a record median approval time of under one year in 1998 and exactly a year in 1999 whilst still maintaining a substantial number of approvals*. In terms of median approval times in 1999, the USA was the fastest and Japan the slowest of the authorities. Approval times in Australia and Canada were virtually identical for 1998 and 1999 at approximately 1.4 years, despite the slightly longer review times in Canada during 1995 and 1996.

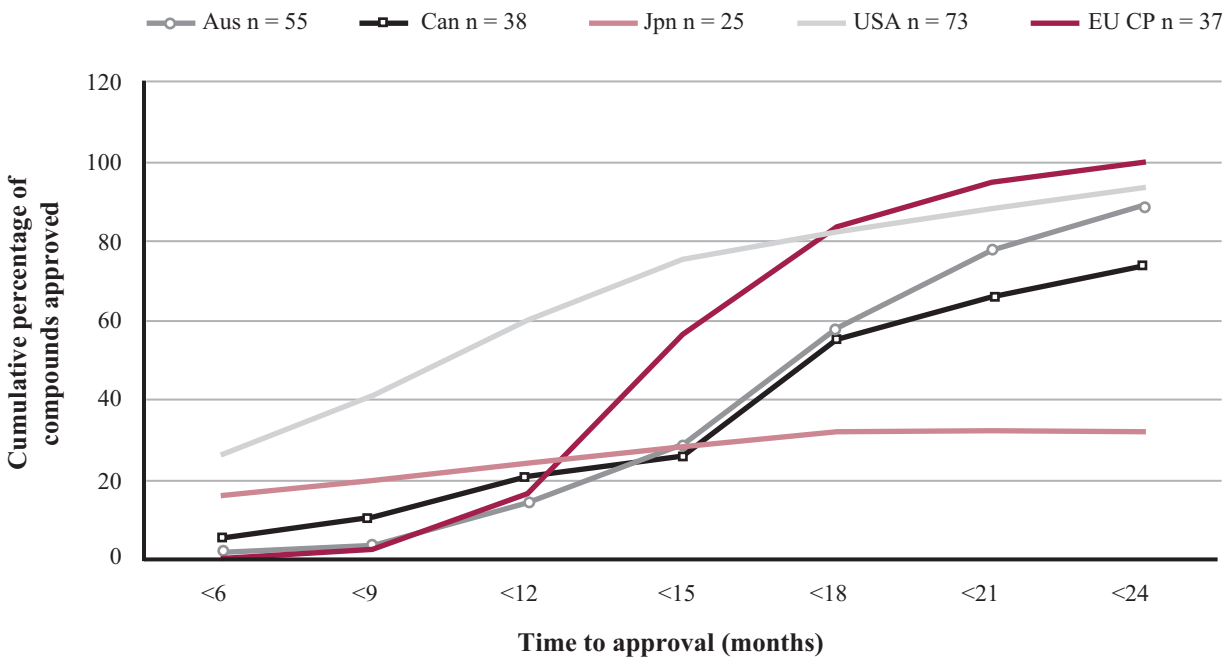
The Japanese Ministry of Health, Labour and Welfare (MHLW) has pledged to shorten review times and in April 2000 introduced a 12 month review 'clock' whereby both the MHLW and sponsor company each have a 12 month target for their respective contribution to the review process for a new drug application. This will undoubtedly place significant demands on the authority given that the median approval time in 1999 was nearly 3 years. However, the recent addition of more staff to the review and consultation divisions is an encouraging sign that the MHLW are committed to increasing the efficiency of their review process.

In Europe, it has been six years since the introduction of the centralised and mutual recognition licensing procedures (CP and MR, respectively) in 1995. The CP has shown a high degree of consistency since 1997 with approval times at around 15 months. In contrast, MR approval times have doubled since 1997 (Figure 1). Both procedures have recently been subject to an operational review commissioned by the European Commission to identify problems and suggest improvements that could be made to the two systems (2). The report found that CP is perceived to be working well. However concerns were expressed about the delays between the CPMP opinion and the issue of a European marketing authorisation by the Commission. There was also general support for the aims of MR and it was noted that the flexibility of this system meets the commercial needs of many companies. Concerns regarding MR include non-adherence to the fundamental concept of mutual recognition, with Concerned Member States (CMSs) continuing to be reluctant to accept the initial assessment of the Reference Member State (RMS).

Marked differences still exist in the relative efficiency of individual regulatory authorities in granting approvals. This most likely reflects differences in the processes employed by different authorities. Such efficiencies have been estimated using the cumulative percentage of approvals over a fixed time period (Figure 2).

* It should be noted that the median approval time for NMEs in 2000 has increased to 15.6 months, as quoted by the CDER, FDA (1).

Figure 2 *Proportion of '98 & '99 approvals granted within 2 years*

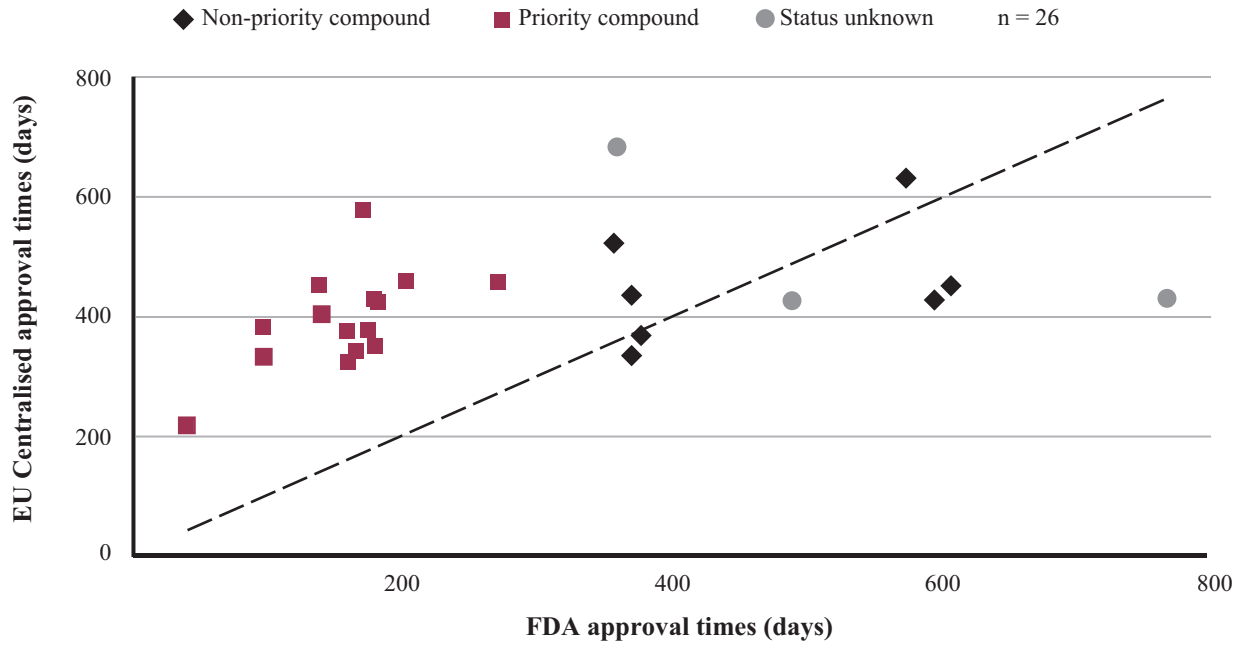


The FDA granted approvals for more compounds than any other authority during 1998 and 1999. Moreover, more than twice as many compounds were marketed in the USA compared with other markets in this period. Yet, the FDA was still seen to maintain efficiency compared with other authorities, granting 26% of its approvals within six months and 60% within twelve months. In terms of approvals made within six months, the FDA far exceeds any other authority. This could be a result of the legislation in the USA which allows certain priority compounds, such as those treating life threatening diseases, to have an expedited review within a target time of six months. However, Figure 2 includes not only review time but also company time, therefore it is not possible to comment on the proportion of priority compounds that have been reviewed within their target time.

The EU CP, despite only being able to approve one compound within nine months, performed well overall, granting all approvals within 24 months. In this respect, the CP could be said to be the most consistent and predictable in the time taken to grant approvals, with the majority (68%) of approvals taking 12 to 18 months. Unlike the USA, a priority review system does not exist in the EU. However there is an accelerated evaluation process for products indicated for serious disease which meet given criteria (EMEA, CPMP/495/96), though details of this are not readily disclosed by the EMEA.

As the industry strives towards a global, harmonised environment, simultaneous submissions must become a feasible reality. Currently, relatively few compounds are being submitted simultaneously to the major markets. Between 1995 and 1999 the number of compounds submitted simultaneously (within one month) to the USA, Europe (CP), Canada and Australia ranged between two and ten per year. Furthermore, simultaneous submissions including the Japanese market are not being regularly achieved. On a more encouraging note, for compounds submitted globally, the time from submission to the first major market to submission to the last major market is getting shorter. The International Conference on Harmonisation recently signed off the Common Technical Document initiative which should also facilitate and encourage global submissions.

Figure 3 *Regulatory approval time for compounds submitted to the USA and the EU via the Centralised procedure within 1 month (1995-1999)*



Access to medicines in the EU and US

As well as companies seeking early market access for their products, ultimately, patients also want access to high quality new medicines as quickly as possible. At present access to medicines in different markets is a major issue and appears to vary geographically.

Comparisons are often made between two of the largest markets in the world, the EU and the USA. Between 1995 and 1999, 26 reviews had been completed for compounds submitted to both the EMEA and FDA within one month (Figure 3).

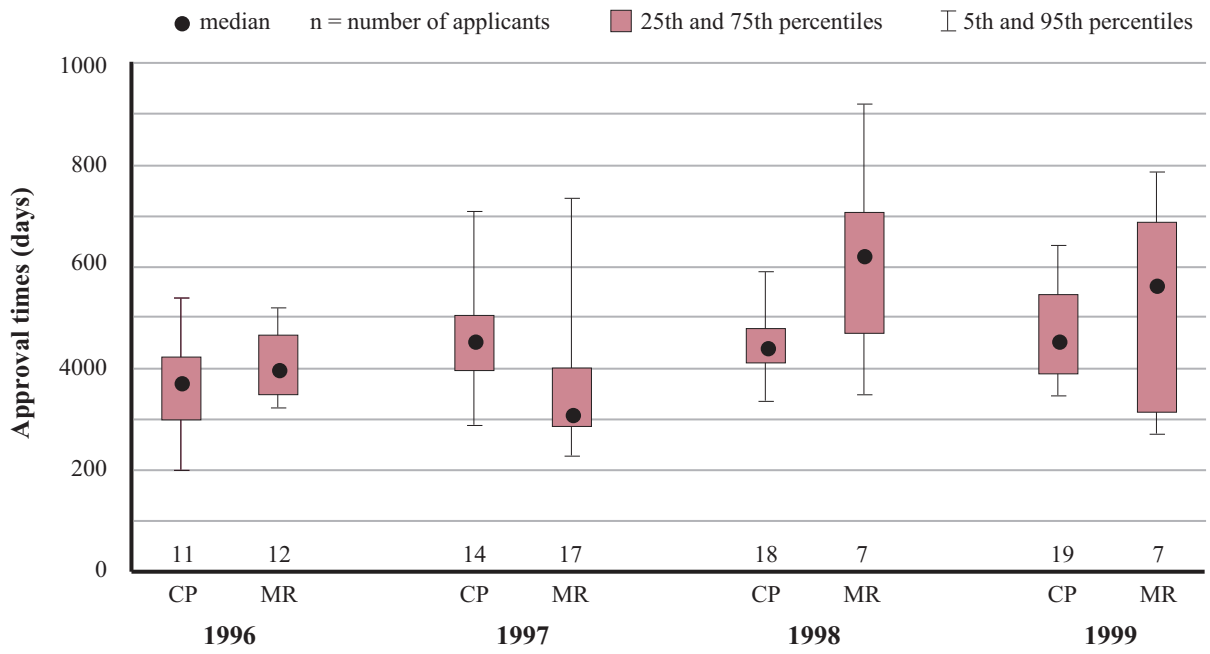
Twenty out of the 26 compounds were approved by the FDA in a shorter time than the EMEA and yet nine had been submitted to the EMEA before the FDA. Of these nine, seven compounds had shorter review times at the FDA, where all but one compound was granted a priority review. This illustrates the impact of different processes in place across regulatory authorities, but should differences in process cause differences in patient access to new medicines?

A closer look at the EU

Establishment of the EMEA in 1995 was an attempt to unify regulatory practices within the EU, although there remain obvious differences between the two licensing procedures. Figure 4 uses a box and whisker plot to illustrate the distribution of approval times through the MR and CP between 1996 and 1999. Ninety days (the time given for CMSs to decide to either accept or reject the decision of the RMS) have been added to the mean approval dates of RMS reviews in order to make the data comparable to the CP.

Predictably the CP, with its more transparent and clearly defined timelines, has more consistent approval times than MR. In contrast, MR approval times have increasingly become more widely spread. This could be due to the nature of MR and its dependence on input from numerous agencies within the EU.

Figure 4 *Comparison of approval times through Mutual Recognition and the Centralised Procedure 1996-1999*

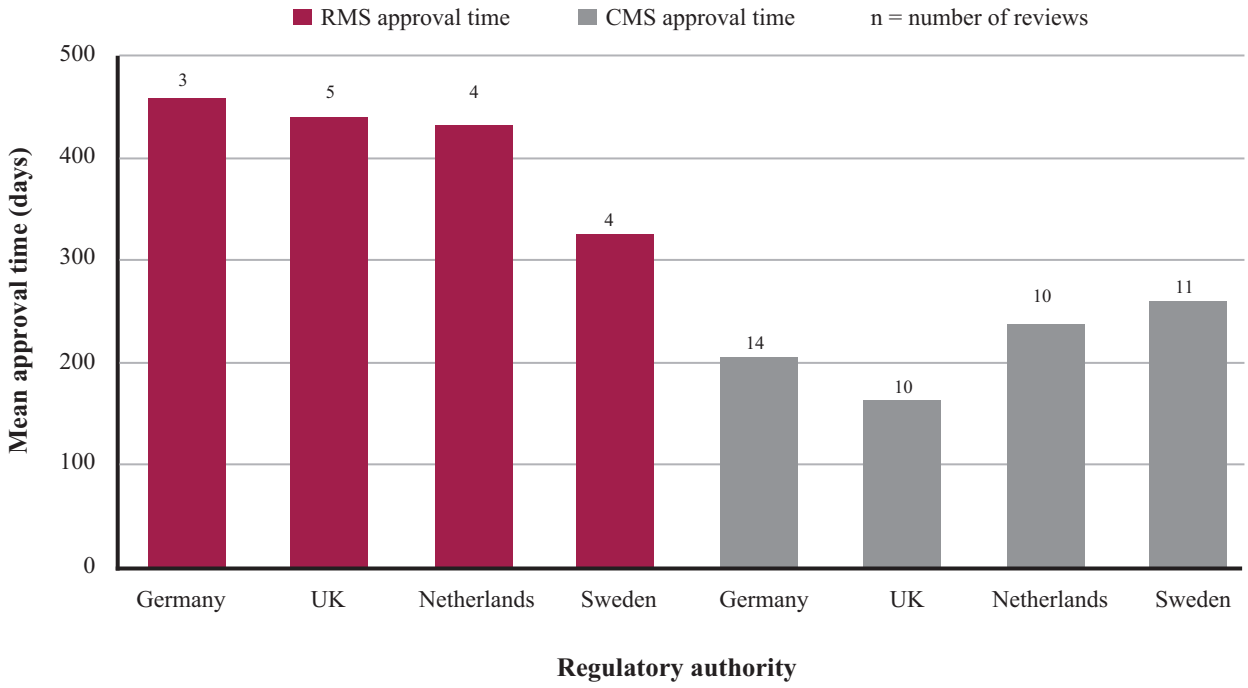


There are obvious differences between individual regulatory authorities involved in EU procedures, both when acting as RMSs and as CMSs, despite their close links and thus expected consistency (Figure 5). Mean RMS approval times in Germany, the UK and the Netherlands during 1998 and 1999 were almost double the recommended best practice time of 240 days, leaving much room for improvement. Sweden had the quickest mean review time of 325 days when acting as RMS. However, consideration needs to be given to the small numbers of approvals in this data set which allow outliers to bias the mean time.

The 30-day best practice target for issuing an authorisation, which follows on from the 90-day allowance to accept or reject the RMS decision, has yet to be achieved by CMSs. Many regulatory authorities are exceeding this target considerably. The UK performed better when acting as a CMS than as a RMS taking on average 164 days to mutually recognise Marketing Authorisations granted by the RMS.

There appears to have been a shift in the selection of RMS since MR was introduced in 1995 (Figure 6). A transition has taken place whereby the UK no longer dominates the market, but now shares equal selection with Sweden. The reasons for Sweden's increased popularity is not known. In addition, the number of RMS reviews initiated in 1998 and 1999 combined was half that it was during 1995 and 1996. This could indicate that either the number of NASs reviewed annually is declining, or that MR in the EU is on the decrease.

Figure 5 *European agency Reference Member State and Concerned Member State approval times for '98 & '99*



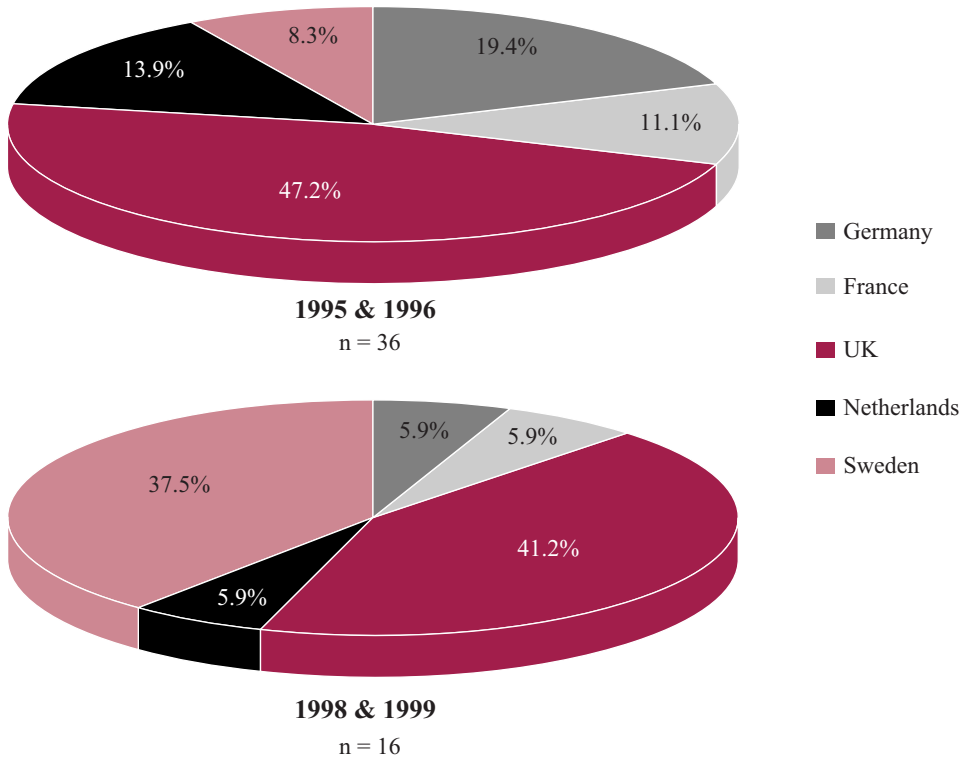
Conclusion

In order to meet the ever increasing expectations of both the competitive industry and the general public for quick access to high quality medicines, it is necessary for regulatory authorities to continue striving towards a more homogenous review process world-wide. Furthermore, this process needs to be efficient but not compromised in quality.

Despite the underlying factors which influence overall approval times, such as culture, conduct, management, or resources, is it possible to further improve regulatory approval times, or have authorities reached their optimum performance targets?

It is important to continue monitoring regulatory authorities' performance to ensure efficiency is maintained and to highlight the areas in need of further improvement. The ultimate focus is to provide all patients with timely access to safe and effective new medicines.

Figure 6 *Changes in the choice of reference member state for applications through the mutual recognition procedure*



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References

(1) Approval Times for NDAs and NMEs Approved Calendar Years 1986-2000, CDER, FDA http://www.fda.gov/cder/rdmt/CY00NDAAP.HTM

(2) Report on the 'Evaluation of the operation of Community procedures for the authorisation of medicinal products' carried out on behalf of the European Commission by Cameron McKenna and Anderson Consulting. Available on the European Commission Enterprise DG Pharmaceuticals and Cosmetics web site http://dg3.eudra.org

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