



R&D Briefing

Mapping the Milestones

Similarities and Differences in Review Processes

'Generic' regulatory review process

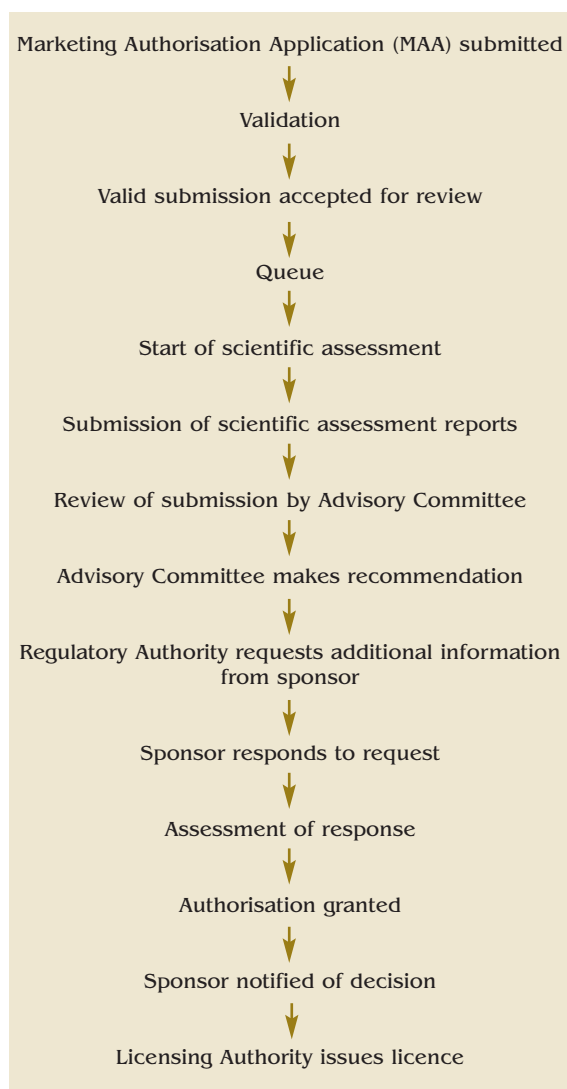


Figure 1 The above flow diagram represents the steps that may exist in a typical regulatory review process. Eleven regulatory authorities were asked to identify which of these steps were relevant to their own processes.

- ❑ *Even when marketing authorisation applications occur within a similar time frame, regulatory authorities around the world can exhibit considerable differences in review times. To explore the reasons for such differences, identification of transparent, defined stages within the regulatory review process, that could be benchmarked across the agencies, has been advocated.*
- ❑ *Responding to this view, expressed by industry and regulatory representatives alike, CMR International initiated a study to characterise the key milestones used in the review processes of nine major authorities.*
- ❑ *Will the characterisation of milestones allow more accurate comparisons of varying review processes? Are there many milestones common to all authorities? Once the milestones are established, can key performance indicators and timelines for the review process be determined?*
- ❑ *In addressing these issues it is hoped that the study will be the first step towards conducting a full-scale benchmarking exercise across review processes worldwide. The information so obtained will provide a powerful tool for focusing regulatory performance improvement initiatives and for evaluating progress once changes have been made.*

Perspective

Past attempts to compare the review processes of different regulatory authorities^{1,2,3} have been hampered by insufficient public information, together with the complexity of the processes themselves. Even though, for some authorities, review performance is becoming more transparent, the lack of uniformity between countries puts considerable limitations on the interpretation of differing review times.

The natural tendency to compare performance, whatever the field, is augmented by a desire to understand the reasons behind marked differences in review times, even when submissions for the same compound are made within a similar time frame (CMR International R&D Briefing No 10). In order to do so, it is necessary to identify transparent, defined stages in the review process that could be benchmarked across authorities; this approach was advocated by a number of regulatory and industry representatives at the eleventh CMR International workshop⁴.

The CMR International Initiative

The Centre responded by conducting a questionnaire-based survey relating to the procedures involved in producing a national licence for a) a new active substance (NAS) and b) a major variation to an existing marketing authorisation. Of the 11 regulatory agencies approached (Table 1), nine participated.

Table 1: Regulatory agencies invited to participate in the survey

Regulatory Authority	Country
Therapeutic Goods Administration (TGA)	Australia
Health Canada, Therapeutic Products Directorate (TPD)	Canada
European Medicines Evaluation Agency (EMA)*	European Union
French National Medicines Evaluation Agency (FMA)	France
Federal Institute for Drugs and Medical Devices (BfArM)	Germany
Italian Ministry of Health (IMH)	Italy
Ministry of Health and Welfare (MHW)	Japan
Medicines Evaluation Board (MEB)	Netherlands
Medical Products Agency (MPA)	Sweden
Medicines Control Agency (MCA)	UK
Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER)	USA

* Questioned on the processes employed for the Centralised procedure

Using a list of key milestones, based on a 'generic' review process (Figure 1), respondents identified:

- Milestones applicable to their agency's review process;
- Milestones currently recorded by their agency;
- Performance indicators considered to be important in determining the timeliness, productivity or quality of the review;
- Target times for steps in the review process.

Common Milestones

New active substances

The date of submission of the marketing authorisation application is the key milestone for new active substances, as it is the only milestone recorded by all authorities (Figure 2a). It seems somewhat surprising that the final step in the authorisation process, issuance of the product licence, is not universally recorded; however, in some countries this activity is performed, and hence recorded, by a separate organisation.

The respondent authorities show other similarities, in that all assess the three sections of the dossier (chemistry & pharmacy; pharmacology & toxicology; clinical) in parallel and all but one record submission of the scientific assessment report (ie, the date the reviewer signs it off).

A far greater number of milestones, even if not routinely recorded, are considered applicable to the review process and these could provide the foundation for future benchmarking.

Variations (abridged applications)

Only two milestones are routinely recorded by all seven of the authorities providing information on variations to existing marketing authorisations (Figure 2b). As in the case of NASs, however, a larger number of milestones are considered applicable to the review process.

Key milestones in the review process

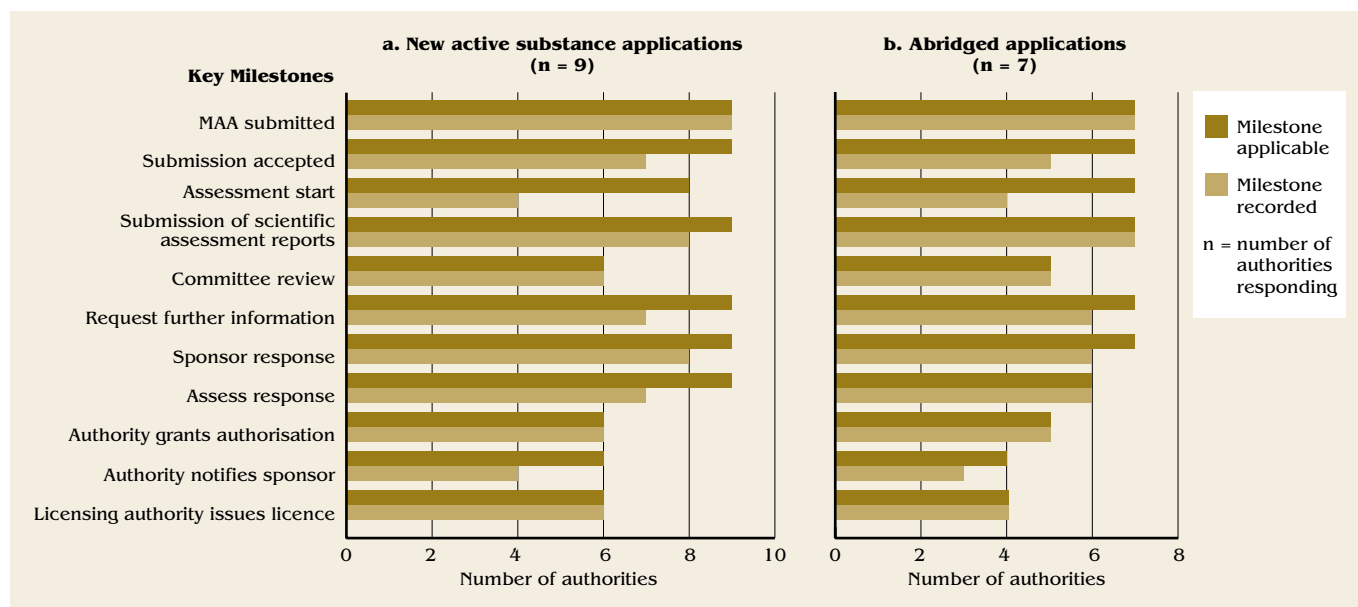


Figure 2 Only one milestone is commonly recorded during reviews for new active substances (NAS) and two for variations to existing marketing authorisations. By contrast, several milestones are considered applicable to each agency's review process.

Target Times

The target times set by the authorities varied enormously, both in terms of the parts of the process assigned targets, and the milestones these contained. In addition, some were quoted in calendar days and others in working days. Consequently, it is not easy to compare target times across authorities.

What Influences Performance?

Depicted in Figure 3 are the quantitative and qualitative influences on either the timeliness, productivity or quality of the review process for NASs, as identified by respondents. Not unexpectedly, the size of the review budget impacts all three factors, according to the majority of authorities.

In general there is a marked similarity between the views relating to NASs and variations to an existing authorisation (abridged applications). There are some differences, however. Time taken for the initial scientific assessment is considered by all authorities to influence the timeliness of NAS reviews, whereas the number of internal reviewers and reviewer expertise are considered to impact abridged applications.

A wide range of criteria influence the productivity of the review process, irrespective of the type of application, with little differentiation in relative importance. However, when it comes to the quality of an NAS review, not surprisingly the number of sponsor meetings prior to the submission, and their outcome, are major influencing factors, together with reviewer expertise and training.

The Next Step

There is clearly a need to benchmark review processes across authorities using the same decision points or events, and this study has shown that such an exercise is feasible. Although, at present, authorities are not collecting and utilising the same data to monitor their own performance, a number of milestones are common to the review processes of all authorities.

Future studies will aggregate data from both companies and regulatory authorities, thereby encouraging partnership and allowing authorities to benefit from each other's performance.

Influences on the timeliness, productivity and quality of the review for NAS applications

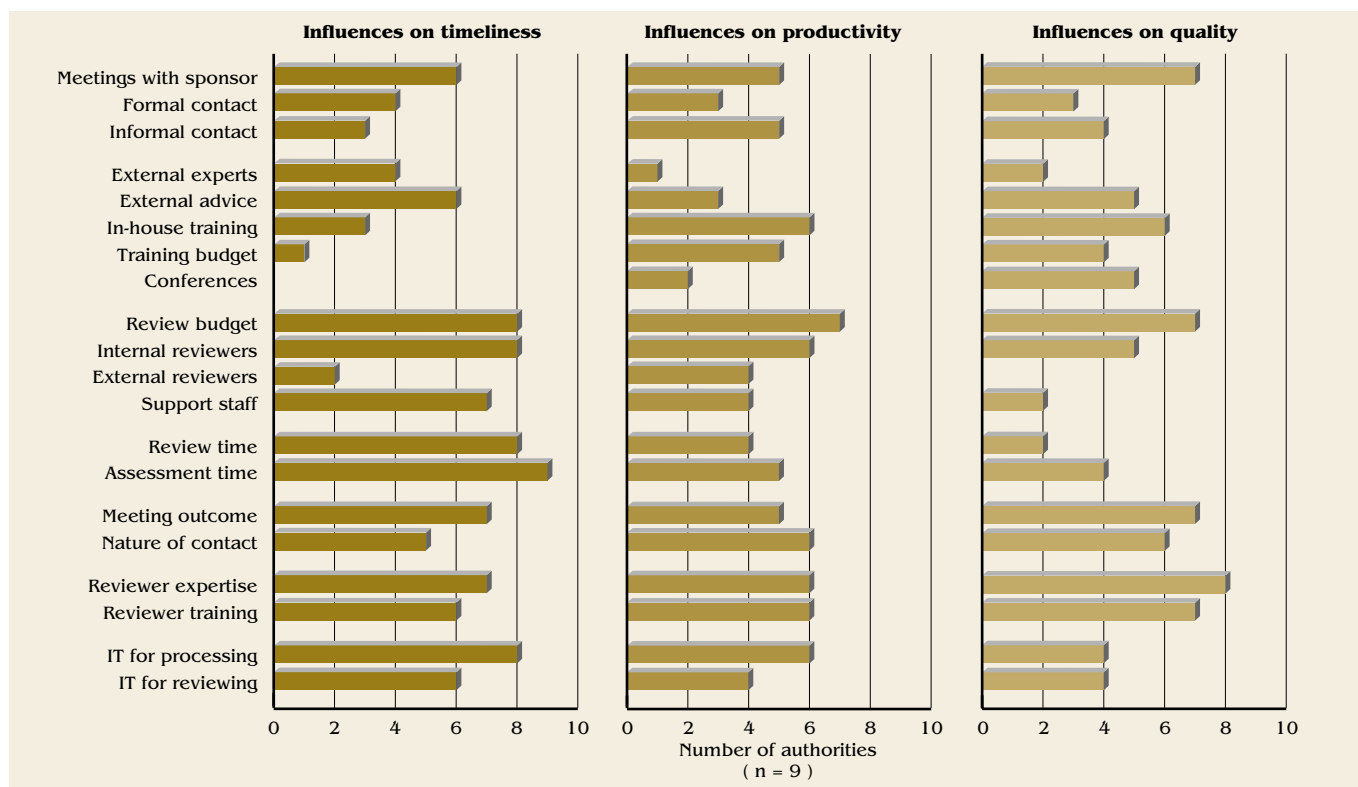


Figure 3 The respondent authorities considered that a number of the factors listed in the questionnaire influenced the timeliness, productivity or quality of the review process. In particular, the size of the review budget was considered to impact all three areas by the majority of authorities.

References

1. Thomas KE, McAuslane N, Parkinson C, Luscombe DK and Walker SR. A study of trends in pharmaceutical regulatory approval times for 9 major markets in the 1990's. *DIA Journal* (in press).
2. Pieterse, EA. A comparison of regulatory approval times for new chemical entities in Australia, Canada, Sweden, the United Kingdom and the United States. *J Clin Pharmacol* 1992 32: 889-896.
3. Harvey C, Lumley, CE and Walker SR. A comparison of the review of a cohort of NCEs by four national regulatory authorities. *J Pharm Med*, 1993 3: 65-75
4. Lumley CE. Suggestions that might be considered for improving the review process. In: Lumley CE and Walker SR (eds) *Improving the Regulatory Review Process: Industry and Regulatory Initiatives*, Kluwer Academic Publishers, Dordrecht, The Netherlands, 1996: 119-130.

This Briefing is based on the paper:

KEY MILESTONES IN THE REGULATORY REVIEW PROCESS

by KE Thomas. In: *Improving the Regulatory Review Process: Assessing Performance and Setting Targets*. Edited by N McAuslane and S Walker. Published by Kluwer Academic Publishers, Dordrecht, The Netherlands.

Copies of the book can be obtained from Kluwer Academic Publishers, Order Department, PO Box 322, 3300 Dordrecht, The Netherlands.

September 1997

R&D Briefing 11



Centre for Medicines Research International

Woodmansterne Road, Carshalton, Surrey SM5 4DS, UK

Tel: +44 (0)181-643 4411 Fax: +44 (0)181-770 7958

E-mail: cmr@cmr.org Web Site: <http://www.cmr.org>