

## DESCRIBING DOSSIERS: CHARACTERISING CLINICAL DOSSIERS FOR GLOBAL REGISTRATION

**Table 1** *Number of trials and subjects per dossier*

Twenty-three dossiers for new active substances were submitted between February 1995 and April 1999 for products from nine different therapeutic areas, the largest number of products being for the nervous system.

	Average number of trials per dossier	Average number of subjects per dossier
Phase I	21	434
Phase II	6	696
Phase III	10	3348
Total	37	4478

Clinical dossiers currently contain massive volumes of data; they are costly and time consuming for sponsors to prepare and regulators to review. Global submissions, increasing regulatory requirements and evolving clinical development plans are all potential drivers for the size of the clinical dossier.

Are dossiers increasing in size and complexity? If so, can that increase be contained? What is the perceived value of the contents of the clinical dossier?

As a step towards addressing these questions, CMR International conducted a detailed examination of recently submitted dossiers for new active substances. This indicated a downward trend over recent years in the average number of clinical trials contained within a dossier. By contrast, the number of subjects per dossier remained, on average, the same.

Clinical development strategies are being re-engineered to ensure fewer, more successful trials. But the need to compete in a crowded market continues to put pressure on the size of the dossier.

As clinical development remains a lengthy and costly process it is not surprising that the dossier submitted for regulatory review for a medicinal product is large and extremely complex. However, the industry firmly believes that the size of the dossier has grown dramatically over the past 10 years, according to a recent CMR International pilot study. In a bid to understand more about the perceived value to sponsors and regulatory authorities alike of the trials contained within the clinical dossier, a questionnaire-based survey was conducted amongst 46 pharmaceutical companies.

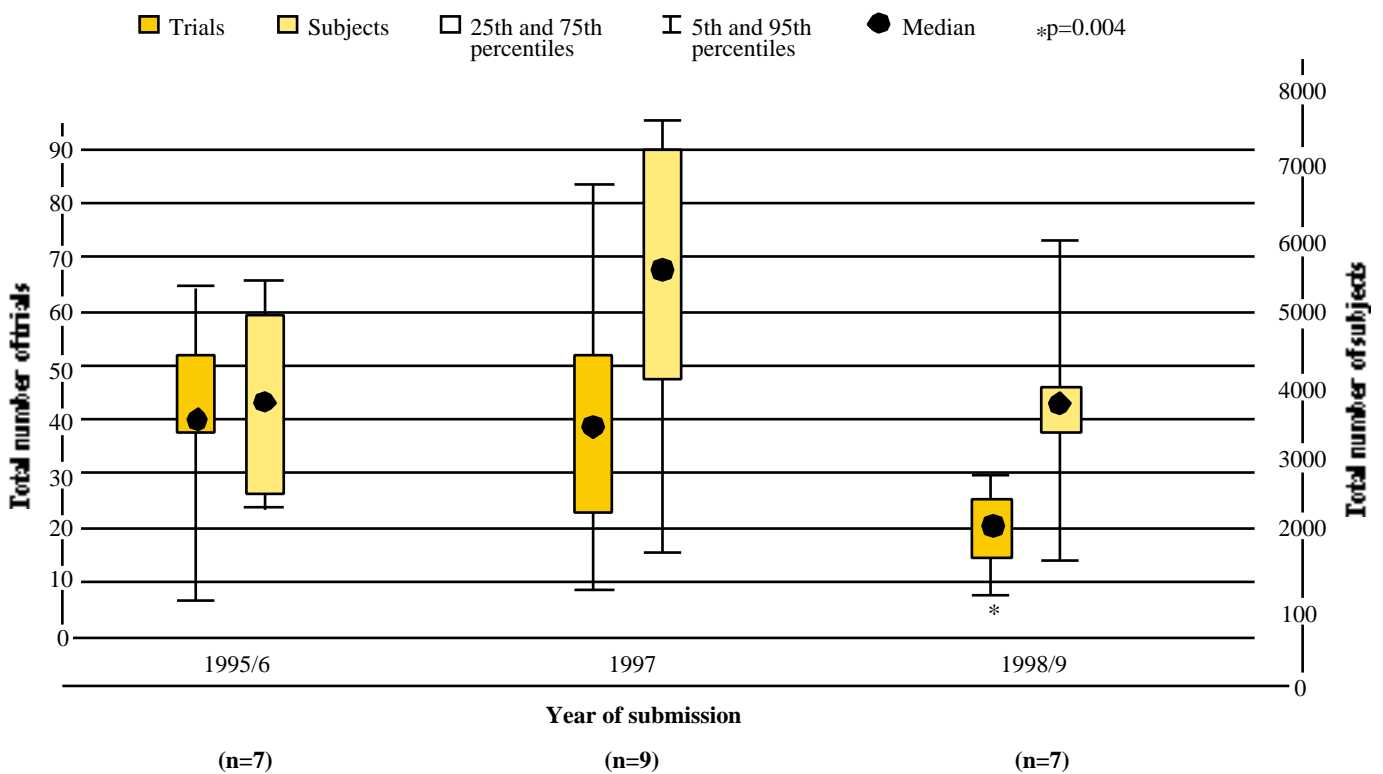
This sought to:

- Characterise and critique the contents of recently submitted dossiers for new active substances (NASs);
- Determine current strategies for reducing the size of the clinical dossier;
- Investigate how clinical development is being re-engineered for the future.

Of the 46 companies asked to participate in this survey, 23 were able to provide details of a dossier recently submitted to regulatory authorities in Europe, the USA or Japan. Twelve dossiers sought marketing authorisation for only one indication; nine dossiers were for multiple indications (maximum eight). Each dossier contained, on average, reports on 35 clinical trials relating to an average of over 4,000 trial subjects per dossier (Table 1). As expected, the majority of subjects were included in Phase III trials even though Phase I exhibited the greatest average number (and range) of trials per dossier (median 20).

**Figure 1** *Number of clinical trials and subjects per dossier by year of submission*

There is a downward trend in the total number of trials contained in the dossiers; the fall between 1995/6 and 1998/9 represents a significant decrease ( $p=0.004$ ). No trend in the number of subjects was evident.



## Trends by year of submission

Trends over time were investigated by dividing the 23 dossiers into three roughly equal groups according to their year of submission (Figure 1). For dossiers submitted in 1995/6 the median number of trials per dossier is 40; for 1997 this figure is 39. However, by 1998/9 there had been a significant fall ( $p=0.004$ ) in the total number of trials, the median per dossier being 21. This downward trend was apparent across all phases of clinical development, suggesting a reversal of the pattern of increasing numbers of trials per dossier seen during the late 80s and early 90s.

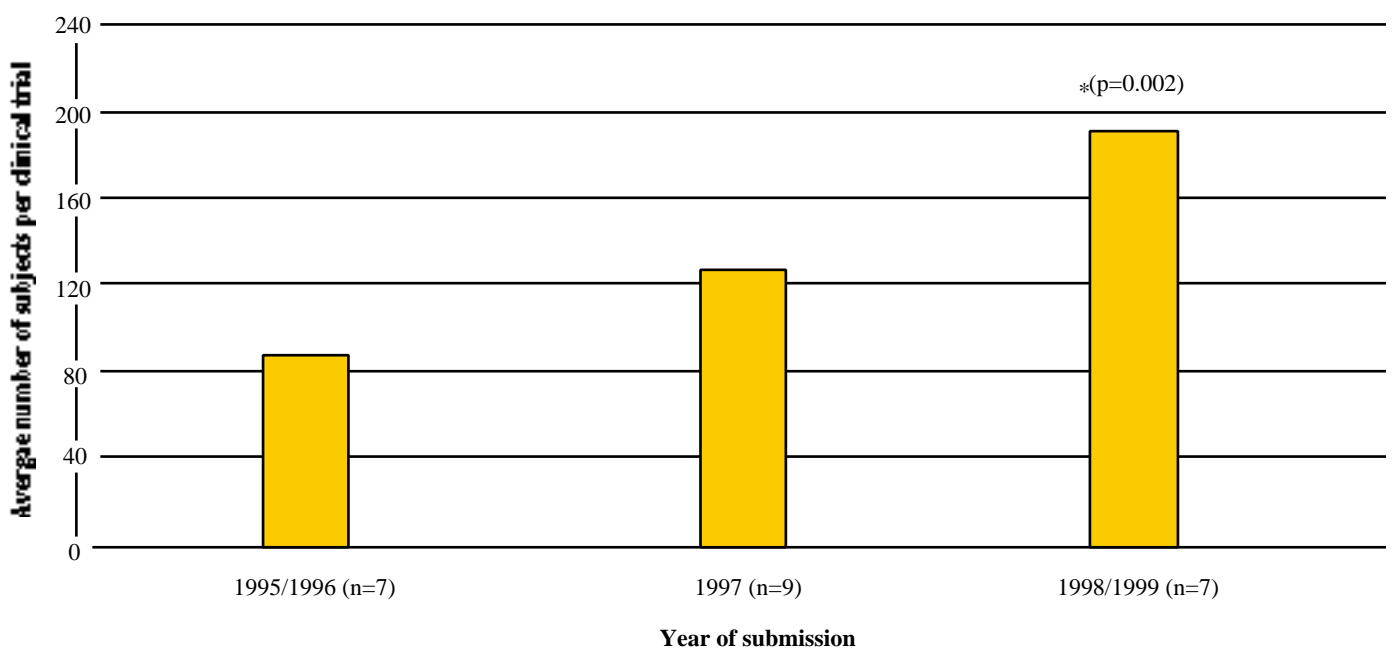
By contrast, no trend was evident in the total number of subjects studied for each submission (Figure 1), the medians being 3864 for 1995/6, 5582 for 1997 and 3750 for 1998/9 submissions. This lack of change, coupled with the decrease in number of trials over time, results in a doubling of the average number of subjects per clinical trial from 89 in 1995/6 to 191 in 1998/9 ( $p=0.002$ ) (Figure 2). It appears, therefore, that in all phases fewer but larger studies are being conducted to generate the data necessary for a submission.

## Nature of the trials

The role of each clinical trial is key in any assessment of dossier contents. Over 50% of Phase III trials were regarded as pivotal for regulatory approval. The remainder, generally conducted for commercial reasons, might include trials in special patient populations and comparator controlled trials. The impact of these studies is to increase the average number of trials per dossier. Interestingly, dossiers which included pharmacoeconomic studies contained fewer trials, but not subjects, in total than those that did not.

**Figure 2** *Number of subjects per clinical trial by year of first submission*

The decrease in the number of trials in 23 dossiers over the period 1995 to 1999 accompanied by no change in the average number of subjects, results in a doubling of the average number of subjects per trial over the same period, a significant increase ( $p=0.002$ ).



Electronic technologies are being used increasingly for submissions to regulatory authorities. Of the 23 dossiers, those submitted most recently were more likely to be completely, or in part, in an electronic format (Figure 3).

This approach has numerous potential benefits to both industry and regulators which in turn may have an impact on the speed of gaining marketing approval.

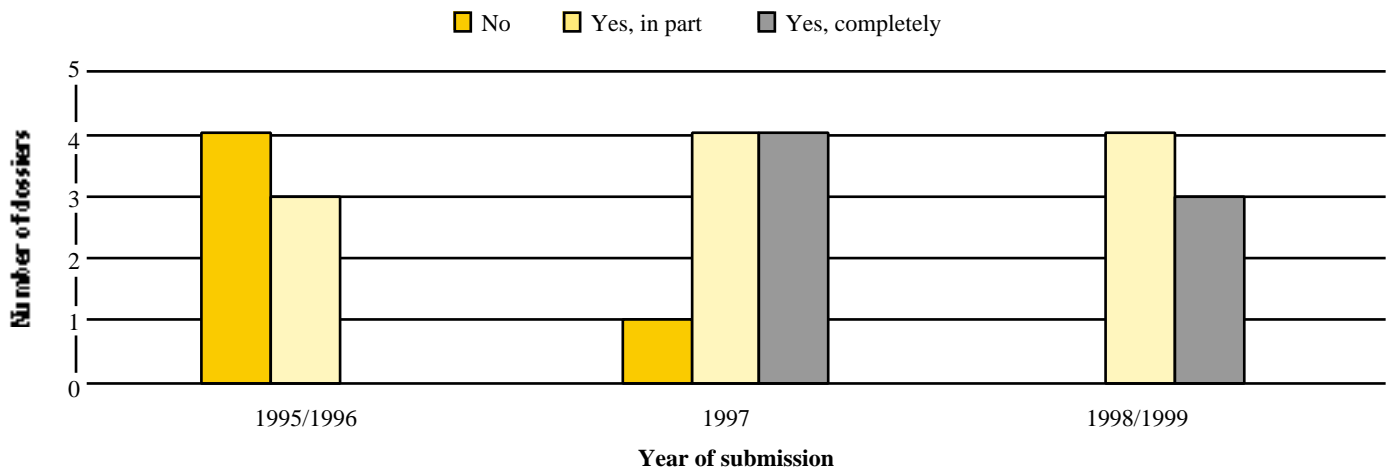
In future, therefore, the size *per se* of the dossier may not be the primary issue if dossiers are submitted electronically.

Commercial pressures from the need to differentiate a product in the crowded and highly competitive market place have, at least in part, been responsible for past increases in the size of the clinical dossier. The majority of pharmaceutical companies have therefore re-engineered their clinical development strategies over the past five years in an attempt to conduct fewer more successful clinical trials. In the future, better planning of clinical development programmes to truly embrace global practices, is expected to have a positive impact on the size of the clinical dossier by reducing the number of subjects studied and trials conducted.

This survey lays the foundation for progress towards dossiers that meet the needs both of industry and regulatory authorities.

**Figure 3 Was the dossier submitted in electronic format?**

Eighteen of the 23 dossiers were submitted either in part or completely in an electronic format, with similar numbers submitted to the USA(8 dossiers) and Europe (10 dossiers). Half the dossiers submitted to the USA and 30% of those submitted to Europe were fully in electronic format.



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