The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

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Performance indicators for the EMEA in 2003

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.eu.int http://www.emea.eu.int

Introduction

This report gives key performance measures in the handling of a range of scientific procedures, co-ordinated by the EMEA.

The report focuses on the scientific review of marketing authorisation applications (pre-and post evaluation human units), scientific advice/protocol assistance and orphan designations. The quantitative data are defined, e.g. number of positive opinions, withdrawals etc.

Against the background of these hard data, it is also attempted to capture indicators of quality of the applicants' dossier and the work of the scientific committees, the CPMP and the COMP.

1. Pre-Authorisation Activities

1.1. Scientific Advice and Protocol Assistance

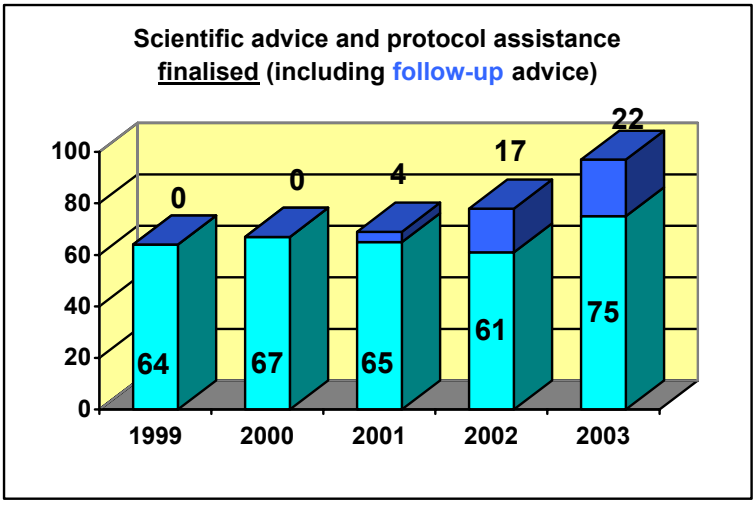
1.1.1. Number reviewed and Time to advice

In 2003 there have been 97 Scientific Advice/Protocol Assistance given by the CPMP (Protocol Assistance was given to 25 products).

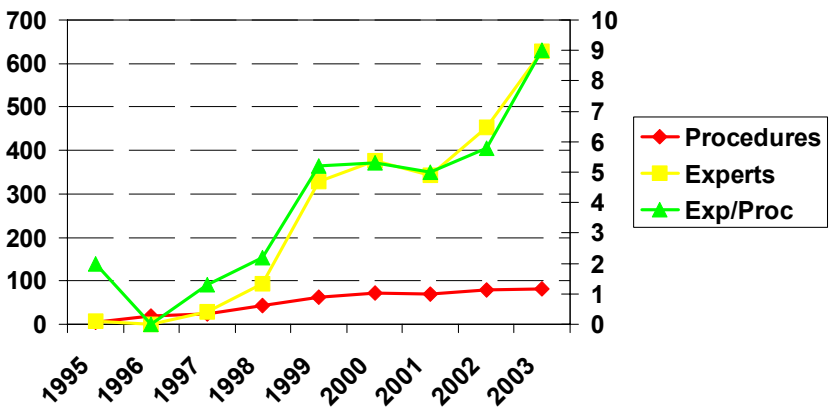
Timelines for the scientific advice/protocol assistance procedures improved in 2003 thanks to the introduction of the new procedure where the Scientific Advice Working Group (SAWG) meets for two working days, two weeks before the CPMP.

The mean duration of the procedure and adoption of the advice letter was 82 days, down from 87 days in 2002. The improvement would have been even greater if a number of procedures had not lasted 130 days because of the summer break.

Scientific Advice / Protocol Assistance
Finalised advice (years 1999-2003)



It is notable that the number of experts involved in each procedure has increased with time such that in 2003 the average number of experts is 9 per scientific advice. This reflects the agency's desire to involve more EU experts in its work, although few of them are external to regulatory authorities.



1.1.2. Customer Satisfaction

In 2003, the EMEA sent a questionnaire to the Companies that obtained an advice in the period January-September 2003. Forty-one responses (63%) were received from the 65 companies that were sent the questionnaire.

KEY TRENDS

The overall number of scientific Advice and Protocol Assistance requests has increased over the past year: for the reference period, the number of advices was 69 in 2003 compared to 56 in 2002.
The general satisfaction with the procedure is high: 85.4% of the companies declared to be satisfied or very satisfied. However, there is room for improvement with regard to the involvement of appropriate expertise in specific fields, and for the clarity of the written advice letters.

The discussion at the oral explanation was found useful by almost all companies who had an OE (97%), but some (31%) pointed out the need for additional expertise for the oral explanation.

Regarding the revised timelines, companies find the timelines acceptable (16) or too long (24).

The high level of satisfaction with the EMEA SA team was confirmed: in 2003 95% of companies declared to be satisfied or very satisfied with the dialogue with the EMEA project manager.
Forty-seven per cent of those who had a presubmission meeting found out that the meeting with the EMEA helped to identify additional issues initially not considered by the company.

1.2 Orphan Medicines designation

1.2.1. Number reviewed and adherence to regulatory timelines

Since the COMP started its activities in April 2000, there have been 187 positive and 5 negative COMP opinions.

	Positive COMP opinions	Applications withdrawn	Negative COMP opinions	Designations granted by the Commission
2003	54	35 (39%)	1	45
2002	43	24 (34%)	3	49
2001	64	25 (28%)	1	64
2000	26	3 (10%)	0	14
Total	187	87 (31%)	5	172

The main reason for failed orphan drug applications was failure to demonstrate that the applied condition met with the prevalence criterion of affecting less than 5 in 10 000 EU citizens.

Concerning the designation procedures, there was 100% adherence to the 90-day timeline in 2003, as was the case from the outset of the procedure.
The Average time from Commission receipt of Opinion to Commission Decision was 44 Days (up from 41 days in 2002). The overall duration of the procedure remains therefore below 120 days.

1.3 Initial Evaluation of Applications for Marketing Authorisation

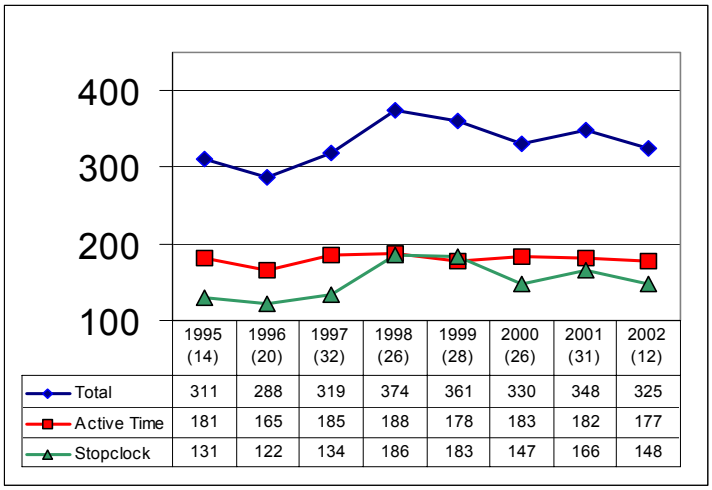
In this section particular attempts have been made to to capture indicators of quality of the applicants' dossier and the work of the CPMP from 1995 or 1998 and until July or October 2003 depending on the cut-off time for the analysis. Some of these data was also presented during the EFPIA info-day in October 2003.

1.3.1. Adherence to regulatory timelines and review times

To study trends in review times throughout the years, approved products have been grouped by year of start of the application (and not by year of outcome). This approach allows to study the performance of the system at a specific point in time, minimising the influence of past performance. The last year of start considered was 2002, and this includes all applications that reach an outcome by July 2003.

The time spent on reviewing marketing authorisations has remained rather stable since 1995. The overall time is about one year and the active time and clock-stop respectively remain about 6 months - the active times remaining within the stipulated 210 days. The 2 figures below show the review times for applications that started their review between 1995 and 2002 and that reached a positive opinion by July 2003 (cut-off date for the analysis). There was also much variability particularly for the clock stop time that varied from a couple of weeks up until over a year in a few cases (data not shown).

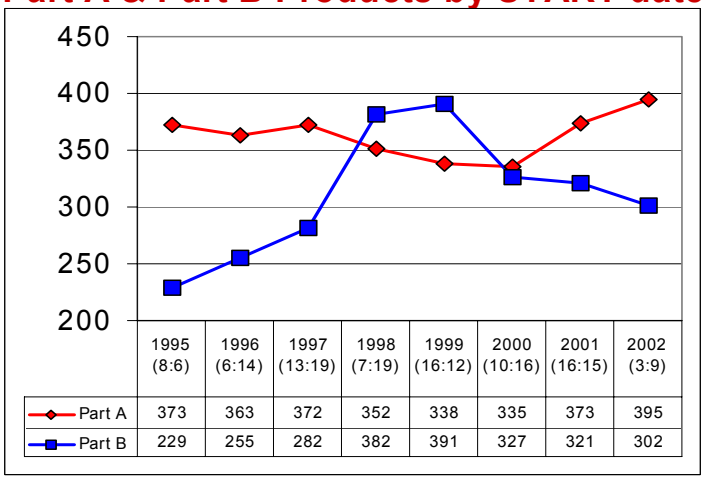
Average Total Time, Active Time, Clock Stop
All Products by START year



	1995 (14)	1996 (20)	1997 (32)	1998 (26)	1999 (28)	2000 (26)	2001 (31)	2002 (12)
Total	311	288	319	374	361	330	348	325
Active Time	181	165	185	188	178	183	182	177
Stopclock	131	122	134	186	183	147	166	148

A relative increase in the review time (i.e. clock stop) for list A products is now being seen. It is thought that this reflects the increasingly more complicated nature of these products.

Average Total Time
Part A & Part B Products by START date



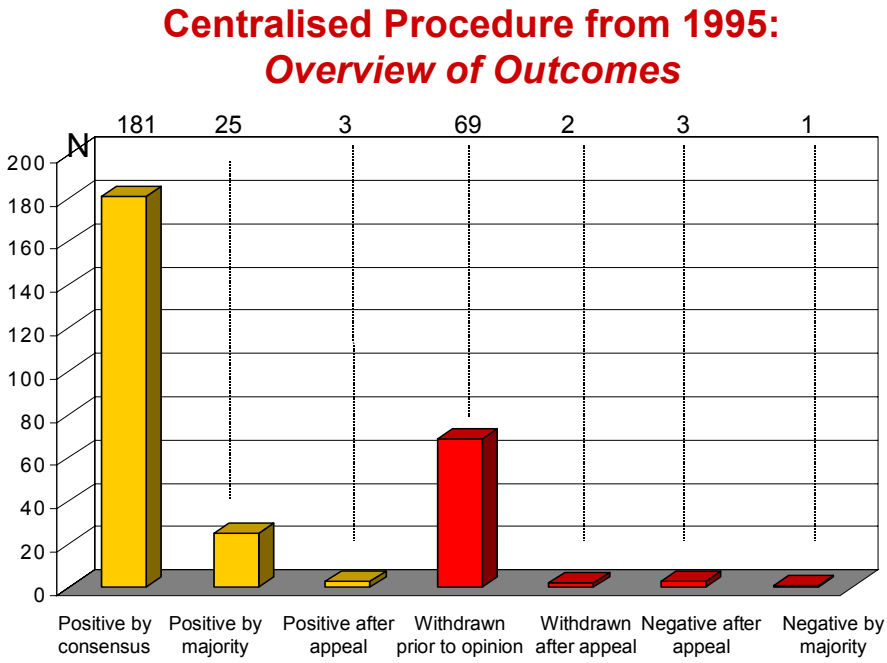
	1995 (8:6)	1996 (6:14)	1997 (13:19)	1998 (7:19)	1999 (16:12)	2000 (10:16)	2001 (16:15)	2002 (3:9)
Part A	373	363	372	352	338	335	373	395
Part B	229	255	282	382	391	327	321	302

The review time for some applications in the HIV/AIDS and in the cancer areas, have been particularly short; e.g. Glivec intended for the treatment of leukaemia was approved after 119 days of CPMP review with no clock-stop needed for the company.

1.3.2. Outcomes of Marketing Authorisation Applications

Overall experience:

Outcomes for applications reviewed by the CPMP since 1995 with an outcome until October 2003 shows that most applications (64%) have been approved by consensus and 9% by majority vote in the CPMP.



Approvability over time

The proportion of rejected applications (withdrawn and with negative opinions has remained about 25 – 30% over the years (24% (6/25) during 2003 until October CPMP).

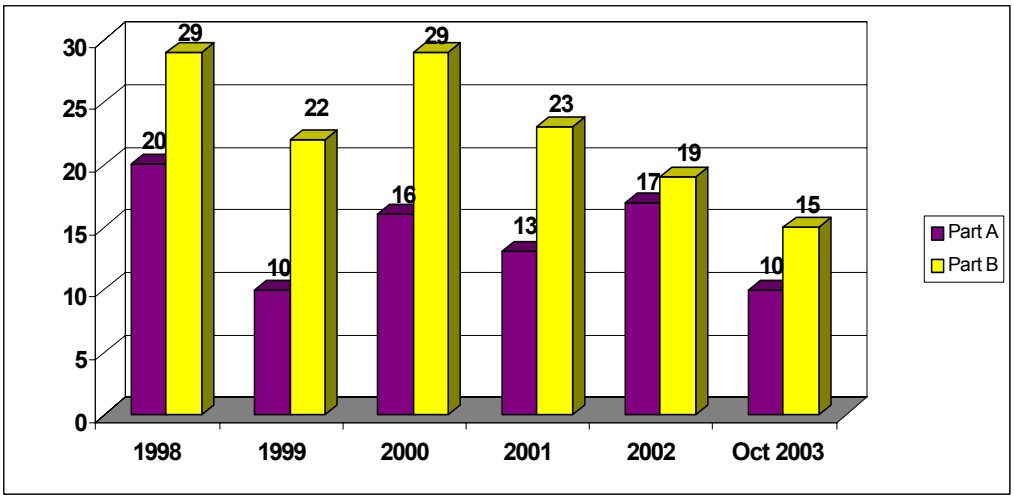
The EMEA has looked into the reason behind negative and positive outcomes by specifically analysing the major objections raised by the CPMP at the time of the List of Questions (Day 120 of the CPMP review). It is notable that issues related to the clinical development are significantly associated with a rejection of an application. Particularly, the lack of adequate randomised controlled clinical trials reduced the probability of a successful outcome by more than 50%.

Although important objections have been raised on many applications after the initial review, most applications have eventually been approved following an additional dialogue between CPMP and the applicants. The approvals frequently follow a restriction of the initially claimed indication(s) or are given under exceptional circumstances, i.e. it has been recognised that the applicant is unable to provide comprehensive information at the time of the marketing authorisation and commits to perform additional studies after marketing. Approval under exceptional circumstances has been given in 40 (19%) of 209 approved applications: particularly in the area of metabolism (29%), Cancer and immunomodulators (28%) and anti-infectives (26%).

List A (Biotech) products

The proportion of list A products submitted to the EMEA have increased over time and as of October 2003 constitutes about 40% (111/284) of those that had an outcome.

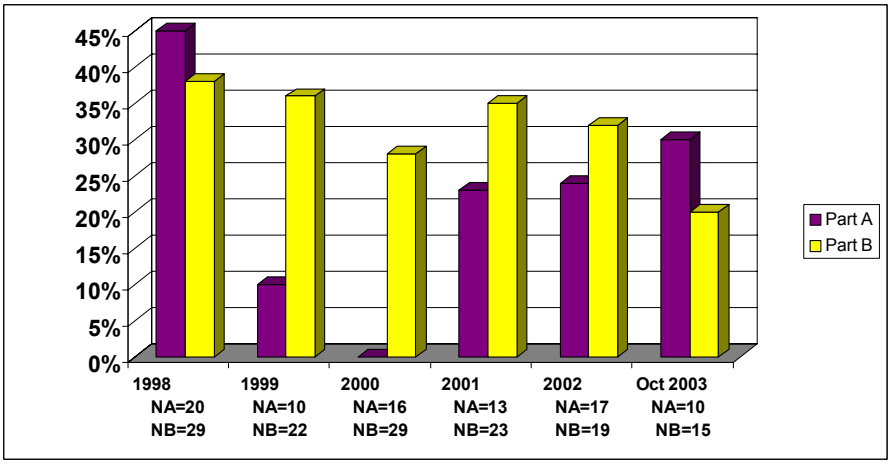
Centralised Procedure from 1998
Number of applications by outcome year according to Part A and Part B



The increased "innovativeness" and hence complexity of these products have increased the review times – as mentioned above – and is also associated with a somewhat increased frequency of rejected applications than what used to be the case.

The last 2 years experience – Jan 2002 until October 2003 - has been that the EMEA has approved 20 biotech products and rejected 7 (26%). Two of these 7 were orphan medicinal products. Scientific advice/protocol assistance was given to 10 (50%) of the approved and 2 of the rejected biotech products.

Centralised Procedure from 1998
Proportion of rejected applications according to Part A and Part B – (N = total applications)

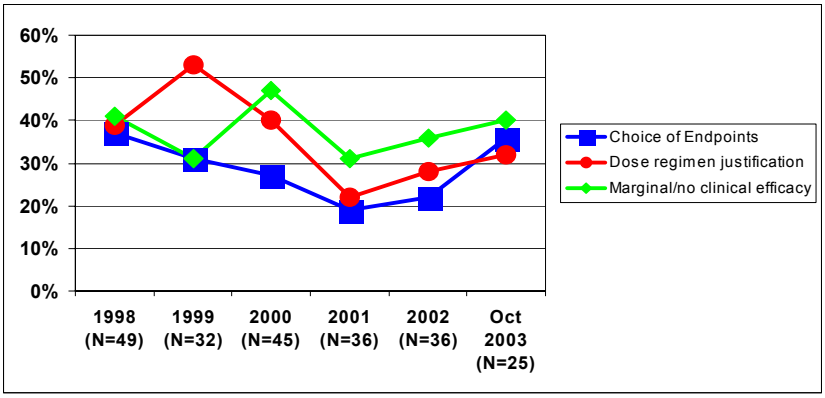


Scientific Reasons behind Rejections

A gap exists between the content of the submitted dossier and the expectations of EU assessors such that most applications are "non-approvable" after the initial review. At this time the CPMP consolidates its view by raising "major objections" against the approval of the marketing authorisation application.

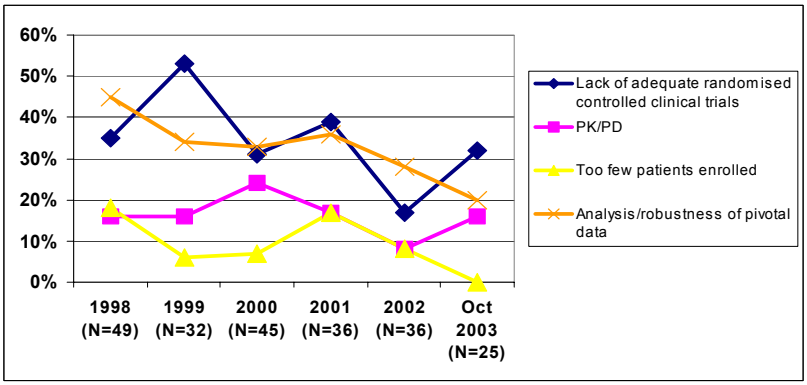
In fact, this "gap" relates to rather crucial aspects of the clinical drug development and the following figures show the incidence of these principal deficiencies by year of outcome.

Centralised Procedure from 1998
Proportion of applications with major objections



It is of interest that although many important aspects on the clinical development (choice of endpoints, dose regimen justification and concerns over the marginal clinical effect) remain frequently raised by the CPMP, fundamental aspects on study design issues (most often the lack of adequate randomised controlled clinical trials) show a tendency to decline. With the improved dialogue between the CPMP and the applicants it is hoped that this trend will be continued

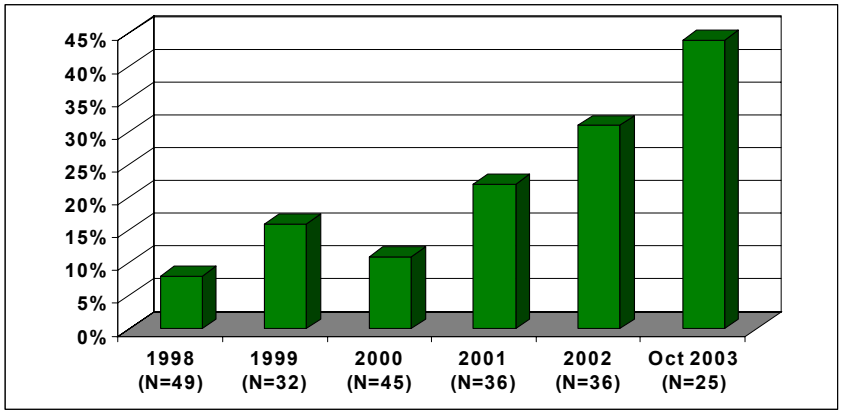
Centralised Procedure from 1998
Proportion of applications with major objections



Impact of Scientific Advice on the probability of a successful Marketing Authorisation Application.

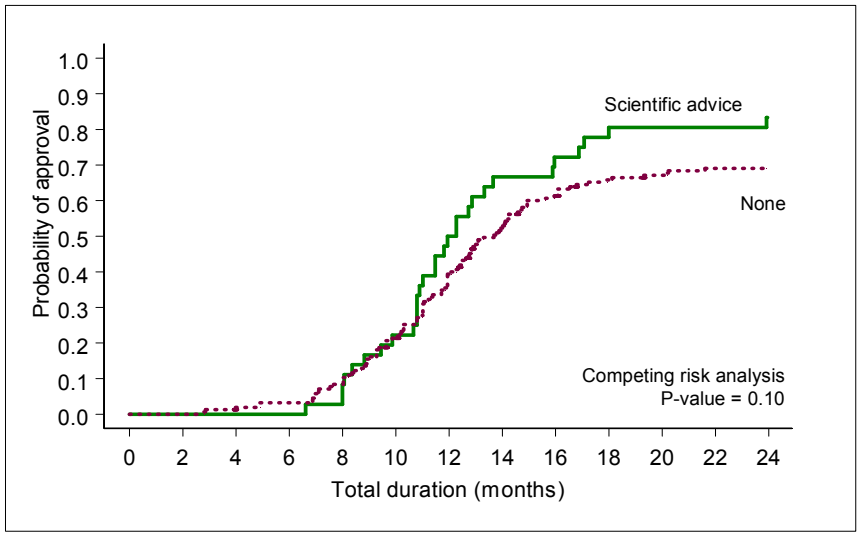
An increasing number of applications have received Scientific Advice prior to Marketing Authorisation Application. More than 40% of applications with an outcome in 2003 have had Scientific Advice prior to submission.

Centralised Procedure from 1998
Proportion of prior Scientific Advice of all MAAs with an outcome



The next figure indicates that the probability of approval is increased for those applications that had a SA prior to the MAA. Also this trend needs to be further monitored.

Impact of Scientific Advice (n=41) on proportion of approvals over time



Orphan drugs

The number of orphan drugs with an outcome in the CPMP scientific review is increasing such that in the year 2003 (until October CPMP), 12 (40%) of 30 applications with an outcome were orphan designated products. In 2002 the proportion of orphan medicinal products was 6 (17%) of 36 applications with an outcome.

From 2001 until 2003 , 22 orphan products had an outcome in the CPMP review. Fifteen (68%) of these were approved. Four (27%) of the approved products were biotech. Eleven (73%) of these 15 products have been approved under exceptional circumstances. Seven (32%) products were withdrawn or had a negative opinion. Only 2 of these 7 orphan products were biotech products as mentioned above.

Seven (47%) of the approved products had received Protocol assistance prior to submission. None of the rejected orphan applications had received protocol assistance prior to submission.

1.4. Quality of submitted dossier of the Marketing Authorisation Application

1.4.1. During June 2002 until May 2003 the Day 70 Assessment Reports from the (Co)Rapporteurs have included a questionnaire related to the quality of the submitted dossier. The results of this survey were presented during the EMEA/EFPIA InfoDay in October 2003.

The overall results of that survey among CPMP (Co)Rapporteurs indicated that there is room for improvement regarding availability of data and analyses in the dossier. In addition some CPMP members were particularly critical about the clinical overview/expert report. It was felt that this document was "not sufficiently critical".

The Common Technical Document (CTD) has been compulsory for marketing authorisation applications from 1 July 2003. The introduction of the CTD has improved the quality of the submission with regard to the layout and presentation of the dossier, but also with regard to the availability of data and analysis expected by the CPMP.

1.5. Customer Satisfaction

A new questionnaire has been developed by the EMEA/EFPIA to measure aspects of communication, guidance and scientific quality of (Co)Rapporteurs and EMEA staff for new Marketing Authorisation Applications and extension of indications.

The overall results of that survey (applications between June 2002 and May 2003) was summarised by industry during the InfoDay in the following way:

•"Pre-submission guidance quite satisfactory
•Rapporteur guidance around List of Outstanding Issues very satisfactory and scored better than EMEA (positive outcomes)
•Overall guidance – quite satisfied. EMEA scored higher than rapporteur (negative outcomes)
•Quality of assessment satisfactory when outcome positive
•However respondents were not satisfied if CPMP raised new issues for OE
•Speed of centralised procedure less of an issue than that of the Decision making phase
•Lowest rating on communication and transparency was on information following the OE"

and concluded upon as follows:

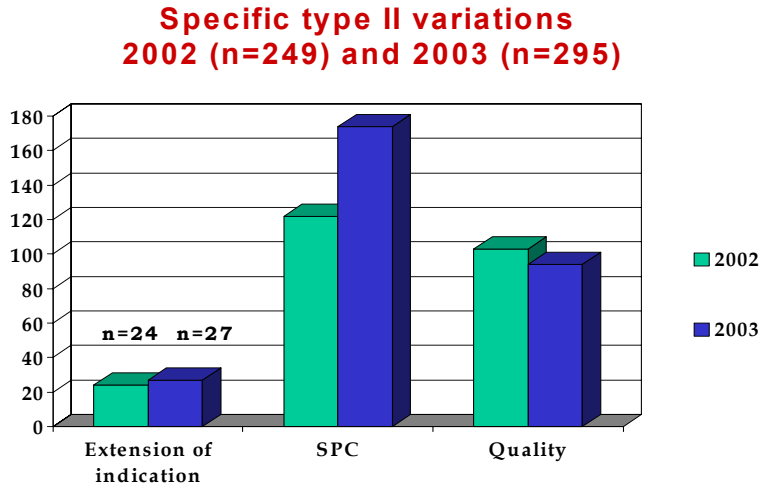
•"Respondents with positive outcomes were satisfied with the centralised procedure
•Biggest difference between the positive and negative outcomes was in the respondents' view of all aspects of the quality of the assessment and discussion at oral explanation
•Questionnaire could be refined to focus on areas of particular interest"

2. Post authorisation activities

2.1. Variations and extensions

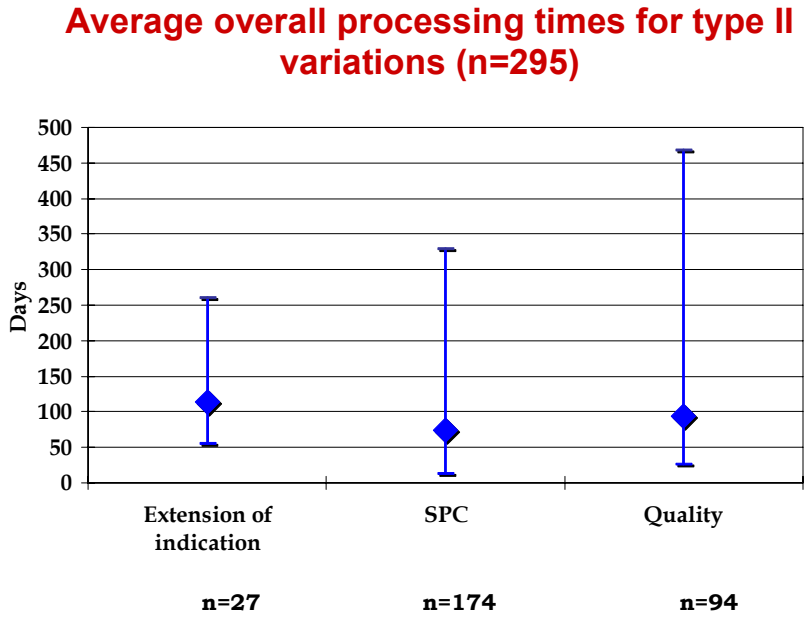
2.1.1 Type II variations and Review times

It can be noted that there has been a 28% increase in post-authorisation applications between 2002 and 2003 (corresponds to a 12-month period from June to May) mostly related to SPC changes and particularly related to adverse events and warnings following PSURs. The results of this survey were presented during the EMEA/EFPIA InfoDay in October 2003.



The average overall processing time varies (figure shows average and range).

67% of the type II variations for "extension of indication" have requests for supplementary information that have impacted on the total review time. In particular, an average delay of about 2 months was noted when issues were raised over the design of the studies in 6 applications.



In October 2003 the legislation governing type I variations was changed to re-classify these procedures into Type IA and Type IB variations and the EMEA will generate separate statistics for these two types in future.

2.1.2. Customer satisfaction

This year a questionnaire has been developed by the EMEA/ EFPIA to measure aspects of communication, guidance and scientific quality of (Co)Rapporteurs and EMEA staff for extension of indications (type II variations) with a positive opinion. There were 26 positive applications between June 2002 and May 2003. Only one application had to be withdrawn prior to opinion.

The results of the survey showed a high degree of satisfaction with the CPMP and the EMEA performance for these (positive) applications.

2.2. Community referrals (article 31)

These referrals are particularly linked to the interest of Community public health related to a medicinal product, which is on the market in the European Union. This is in the light of new data related to quality, safety and efficacy or new pharmacovigilance information.

In 2003 the CPMP issued opinions for 4 article 31 referral procedures. Member States triggered all these referrals mainly due to safety concerns. The workload involved in the management of these procedures was high due to the number of companies and Marketing Authorisation Holders involved.

All article 31 referrals handled by the EMEA complied with the given timeframe of 90 or 180 days according to the legislation.

2.3. Pharmacovigilance

2.3.1. ADR reports entered into EUDRAvigilance database

In 2003, a total of 58,571 adverse drug reaction reports were received by the Agency. 43,554 reports were from ouside the EU, and related to centrally authorised and non-centrally authorised products.

Of non-EU reports a sizeable proportion (48%) were received electronically via the EudraVigilance system.15,017 reports were from EU sources and related to centrally authorised products. Only a small percentage (7%) was received electronically.