European Medicines Agency

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Survey 2006 on the performance of EMEA scientific procedures for medicinal products for human use

Management Board
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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.europa.eu http://www.emea. europa.eu

Executive Summary

Pre-authorisation

Twenty-six products (81%) out of thirty-two that started their review in 2005 received a positive opinion by the CHMP before 31 December 2006. Except for the two article 58 opinions submitted in 2005 there were no medicinal products submitted in that year that were approved within remarkably short review times. This year two products were for the first time approved in accordance with article 14 (7) of regulation EC No 726/2004, so-called "conditional approvals". For both products the Scientific Committee recognised the severity of disease and the medical need. There were nine orphan designated drugs that were approved in this period. The proportion of orphan designated drugs is actually reaching its highest peak in this years' review (35%; 9/26 with positive opinions).

The numbers of SA applications continued to increase markedly and during the October 2006 CHMP meeting the 1000th SA was adopted. During this year the SA procedure underwent important improvements based on the new Regulation (EC) No 726/2004, which allowed for a new Framework for Scientific Advice and Protocol Assistance (EMEA/267187/2005/Rev.1). The proportion of MAAs preceded by scientific advice is 25% and pertained to eight of the thirty-two applications submitted in 2005. Six (23%) of the 26 positive outcomes were preceded by scientific advice and two out of the six negative outcomes had prior scientific advice. Of the two hundred and thirty-six applications with an outcome that have been submitted since 2001 and reached an outcome, the probability of a negative outcome (negative opinion or withdrawal) was 19% (13/68) for applications with CHMP scientific advice compared to 28% (47/168) for application without scientific advice. The actual numbers of major objections (efficacy and safety) appear to be less when SA was given.

The number of applied and approved designations for orphan medicinal products for the third consecutive year exceeded 100. Two negative opinions were adopted in 2006. The average time to COMP opinion and Commission decision was 57 and 25 days, respectively. Last year the figures were 60 and 50 days, respectively. Oncology/immunology make up about 50% of all opinions this year. Half of the designated products are potentially for paediatric use. Both these figures are similar to the figures generated in last year's report.

Post-authorisation

The 2006 exercise showed an increase in the mean overall and active review time compared to 2005 (197 vs. 151 days, and 151 vs. 137 days, respectively). The clock-stop time remained fairly stable. More RSIs were needed, leading to an increase in the number of Major Objections and other concerns raised during the assessment. This might be partially explained by the particularly high involvement of Co-Rapporteurs in the procedures reviewed. No significant association was found between the Major Objections and the review time, or between prior SA and subsequent concerns and procedures outcome. All opinions ended up being positive, including three after Oral Explanation and one after re-examination procedure. Four procedures were withdrawn prior to opinion. Positive opinions were associated with an increased number of post-authorisation commitments compared to the previous exercise. One procedure required the involvement of an Expert Group meeting. The input of specific expertise during the assessment is expected to grow in the future, notably in the form of Scientific Advisory Group meetings (SAGs). Finally, a Risk Management Plan (RMP) was submitted for a third of the extensions of indications adopted (13/39), in accordance with new legislative provisions of Regulation (EC) No 726/2004. Such RMPs were not deemed necessary for the other procedures, for which the new indication was not likely to affect the already known safety profile of the product.

The (Co-)Rapporteurs assessed fairly positively the overall quality of the 28 dossiers for which they provided feedback. The results are comparable to 2005 concerning the presentation and the robustness of the data submitted. The score improved slightly for the quality of the clinical overview compared to the previous survey but this area remains to be improved.

Introduction

This report gives key performance measures in the handling of a range of scientific procedures co-ordinated by the EMEA units for pre and post authorisation of medicines for human use.

The report focuses on the scientific review of marketing authorisation applications, scientific advice/protocol assistance and orphan designations. Some aspects of public heath interest on approved new products are discussed.

An attempt has been made to capture indicators of quality of the different (orphans, non-orphans) applications by looking at outcomes and regulatory concerns raised by the CHMP and also the impact of CHMP scientific advice.

This information will be made available on the EMEA webpage.

I. PRE-AUTHORISATION ACTIVITIES

1. Initial Evaluation of Applications for Marketing Authorisation

General note:

The EMEA Scientific Memory database has been used for these analyses.

The data analysis in this section encompasses applications that **started** their CHMP review in a certain year. For these analysis all applications with an outcome up to 31 December 2006 are included, therefore some applications made in 2005 were still ongoing at this cut-off date.

In the sub analysis of rejected applications the outcome-year rather than the start-year is the basis for the analysis.

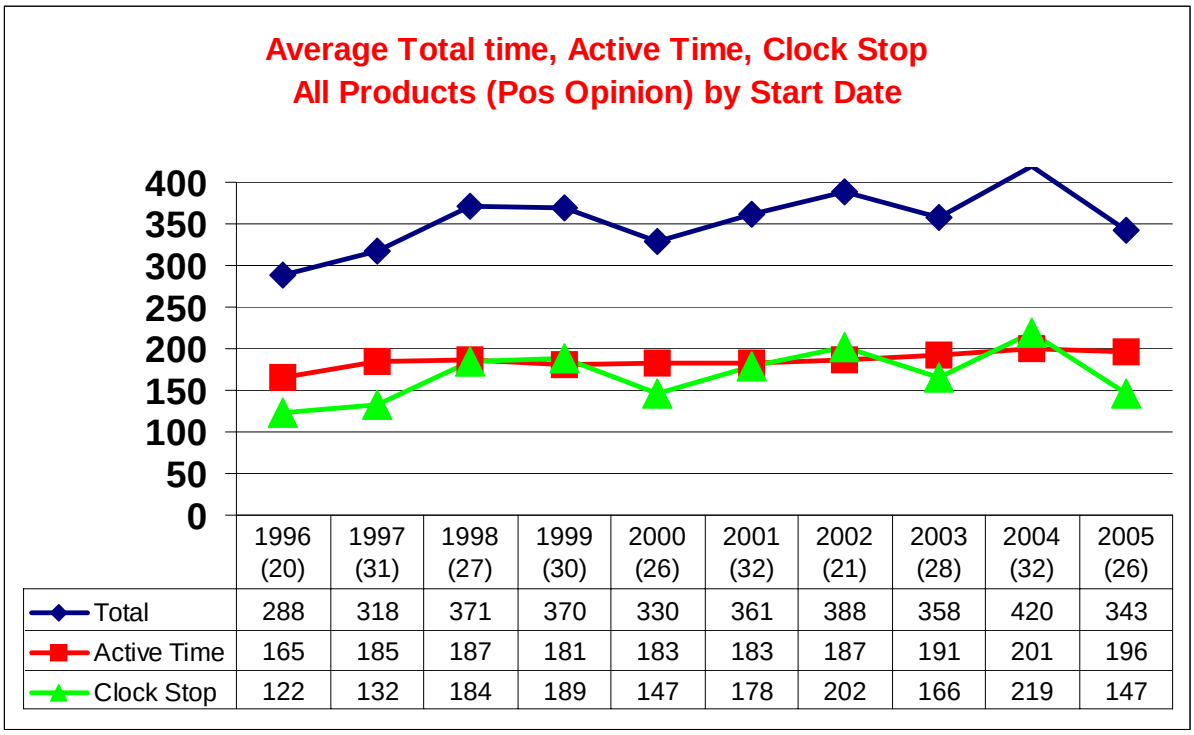
1.2. Adherence to regulatory timelines and review times

Figure 1 and table 1 below show the review times for the applications that started their review between 1996 and 2005 and had a positive opinion by the CHMP.

The overall review time in the CHMP is about one year with the active time remaining within the stipulated 210 days and a clock-stop of about 150 days, which appears somewhat less than in previous years. Since ongoing applications are not included, there is a bias towards applications with shorter review times for the latter year.

Except for the two article 58 opinions submitted in 2005 (see 1.3 *approved products*) there were no medicinal products submitted in that year that were approved within remarkably short review times (table 1). Although the scope of this review is applications made during and before 2005, there were actually a few products that were submitted in 2006 (informed consent/Article 58) which were approved after short review times (<150 days).

Fig. 1



	1996 (20)	1997 (31)	1998 (27)	1999 (30)	2000 (26)	2001 (32)	2002 (21)	2003 (28)	2004 (32)	2005 (26)
Total	288	318	371	370	330	361	388	358	420	343
Active Time	165	185	187	181	183	183	187	191	201	196
Clock Stop	122	132	184	189	147	178	202	166	219	147

1.3. Outcomes of Marketing Authorisation Applications

Twenty-six products (81%) out of thirty-two that started their review in 2005 received a positive opinion by the CHMP before 31 December 2006. Except for one product (Tandemact), these were all approved following consensus views in the Committee. In previous years majority views have been more prevalent. For example, 33 (10.5%) of the 313 approved products between 1995 and 2006 have been approved by majority following divergent views in the Committee.

Approved products

This year two products were for the first time approved in accordance with article 14 (7) of regulation EC No 726/2004, so-called "conditional approvals". For both products (see table 1) the Committee recognised the severity of disease and the medical need. Studies that aimed to confirm the benefits of these treatments were agreed upon.

As was discussed in last years' report, the Committee adopted the first two article 58 (WHO) opinions after a review time of about 60 days. These were Lamivudine/zidovudine and Lamivudine GSK film coated tablets, They were submitted during 2005 to the EMEA/CHMP in accordance with Article 58 of Regulation (EC) No 726/2004, in the context of cooperation with the World Health Organisation (WHO). The products are intended for use in the same indication (part of antiretroviral combination therapy for the treatment of HIV infected adults and adolescents over 12 years of age), with the same dose recommendation and conditions of use, as the centrally authorised product. They are intended to for use exclusively for markets outside the Community.

There are some approvals that are particularly interesting from a public health point of view.

Nexavar (sorafenib) and Sutent (Sunitinib) are antineoplastic agents that act as protein kinase inhibitors and demonstrate compelling clinical efficacy in renal cell carcinoma. This is a form of kidney cancer which is a serious, life-threatening condition with a high unmet medical need. In addition, Sutent demonstrated a high level of efficacy in gastrointestinal stroma tumours.

Gardasil is the first vaccine indicated for the prevention of high-grade cervical dysplasia, cervical carcinoma, high-grade vulvar dysplastic lesions and external genital warts (condyloma acuminata) causally related to Human Papillomavirus types 6, 11, 16 and 18. The indication is based on the demonstration of efficacy of Gardasil in adult females 16 to 26 years of age and on the demonstration of immunogenicity of Gardasil in 9- to 15-year old children and adolescents.

Byetta is the first of a new class; incretin mimetics, intended for type 2 diabetes. This product has distinct advantages compared to other therapeutic principles available, most notably an associated weight loss.

Champix, presents an improvement in efficacy with respect to other currently available pharmacologic treatments for smoking cessation. The medicine is the first in its class with a specific mechanism of action.

Inovelon is indicated in Lennox-Gastaut syndrome, a rare and one of the most severe forms of childhood epilepsy syndrome. The syndrome usually affects children between the ages of 1 and 8 years and continues to manifest into adulthood and has a significant morbidity and mortality rate.

Diacomit is indicated as an adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy.

There were nine (35%) orphan designated products that started their review in 2005 and were approved during 2006 (table 1). These are further discussed below.

Table 1: Applications (n=26) with a positive opinion by *start year* 2005.

Product	Therapeutic Area	ATC Code	Active Time	Clock Stop	SA
Acomplia	Obesity	A	202	142	No
Avaglim	Type II diabetes	A	204	112	No
BYETTA	Type II diabetes	A	208	94	Yes
Champix	Smoking cessation	N	175	71	No
Competact	Type II diabetes	A	204	226	No
Cystadane*	Homocystinuria	A	194	290	No
Diacomit* **	Epilepsy in infants	N	201	317	No
Duotrav	Decrease in intraocular pressure	S	196	82	No
Elaprase*	Hunter syndrome	A	207	87	Yes
Exjade*	Chronic Iron overload	V	174	202	Yes
Ganfort	Reduction of intraocular pressure	S	196	113	No
Gardasil	Human papillomavirus	J	177	44	Yes
Inovelon*	Epilepsy in patients 4 yrs & older	N	208	339	No
Lamivudine	treatment of HIV	J	See text above		
Lamivudine/ Zidovudine GSK	treatment of HIV	J	See text above		
Luminity	Ultrasound contrast-enhancing agent	V	207	314	No
Nexavar*	Advanced renal cell cancer	L	177	34	Yes
Preotact	Osteoporosis	H	224	105	No
RotaTeq	Prevention of rotavirus gastroenteritis	J	190	154	Yes
Savene*	Treatment of anthracycline extravasation	V	204	84	No

Product	Therapeutic Area	ATC Code	Active Time	Clock Stop	SA
Suboxone	Substitute treatment for opiate drug dependence	N	196	78	No
Sutent* **	Malignant gastrointestinal tumour ; metastatic renal cell carcinoma	L	177	34	No
Tandemact	Type II diabetes mellitus	A	196	231	No
Thelin*	Pulmonary arterial hypertension	C	196	92	No
Tygacil	Skin and intra-abdominal infections	J	182	210	No
Zostavax	Herpes zoster	J	202	79	No

* Orphan medicinal product
** Conditional marketing authorisation

Oral explanations (hearings) in front of the Committee can be requested by both applicants and the CHMP and normally occur in the last phase of the assessment, just prior to the adoption of the opinion. These typically focus on some unresolved clinical issues related to efficacy and safety and may play an important role in the decision making process. Nine applications were subject to an oral explanation in this period (table 2). Seven (Acomplia, Competact, Diacomit, Luminity, RotaTeq, Tandemact and Valdoxan) of these oral explanations focussed on clinical efficacy. For Exjade and Mycograb, the oral explanations focused on safety issues.

Table 2: The proportion of applications (*by start date*) that had an oral explanation (hearing)

	1998	1999	2000	2001	2002	2003	2004	2005
Number Hearings	25	16	19	19	11	4	13	9
Total applications	39	38	38	44	29	35	45	32
%	**64%**	**42%**	**50%**	**43%**	**38%**	**11%**	**29%**	**28%**

Negative outcomes (withdrawals and negative opinions)

Six (19%) of the thirty-two applications in this period had a negative outcome (table 3). Two applications received negative opinions from the Committee and four applications were withdrawn by the applicants before the CHMP reached its opinion. One was withdrawn before 20 November 2005, i.e. before the new pharmaceutical regulation came into force. Therefore information about this withdrawal cannot be published on the EMEA webpage. Two products received prior SA from the CHMP.

Table 3: Applications with a start date in 2005

Product	Therapeutic Area	ATC Code	Active Time	Clock Stop	Outcome	SA
Melexanta	Prevention of stroke and other thromboembolic complications associated with atrial fibrillation	B	48	0	Withdrawn - new adverse events	No
Scintimun	Diagnostic agent	V	119	343	Withdrawn - CHMP expressed concerns over the robustness of efficacy and safety data	No
Multaq	Atrial fibrillation	C	177	236	Withdrawn - CHMP expressed concerns over lack of comparative trials and side effects	No
Mycograb*	Invasive candidiasis	L	207	391	Negative opinion - quality and safety concerns	Yes
Vaccine**		J	119	135	Withdrawn prior to opinion	No
Valdoxan	Major depressive disorder	N	207	279	Negative opinion - efficacy concerns	Yes

* Orphan designated medicinal product
**Withdrawn before 20 November 2005

Analysis of applications with outcomes between January 1996 and September 2006

An exploratory analysis was conducted with 390 applications with an outcome between January 1996 and September 2006. "Rejected" applications were defined as outcome of withdrawal or negative opinion. The variables considered included date of outcome, biopharmaceuticals v. new chemical entities (part A v B), orphan designation, scientific advice, ATC code.
In total, one hundred and two (26%) applications were rejected, with ninety-five (24%) withdrawn, and seven (2%) negative opinions. ATC codes A, J, G, and M (genito-urinary system and sex hormones, alimentary tract and metabolism, and anti-infectives for systemic use, musculo-skeletal system, compared to other ATC groups) were associated with lower frequency of rejection (Fig.2). Biopharmaceuticals were less frequently rejected compared to new chemical entities. As a general trend, the frequency of rejection has slightly decreased over time (Fig.3).

Fig. 2: Frequency of rejected applications by ATC code (the number near each label is the no. of applications for an ATC code)

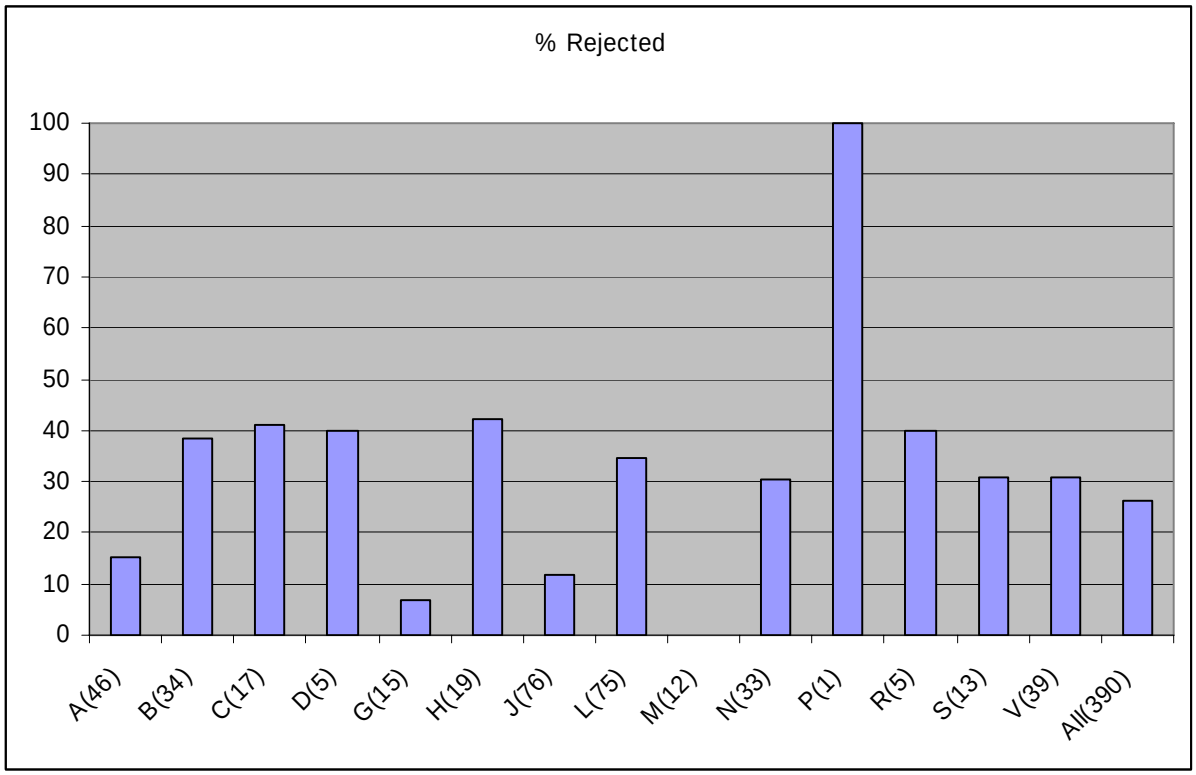
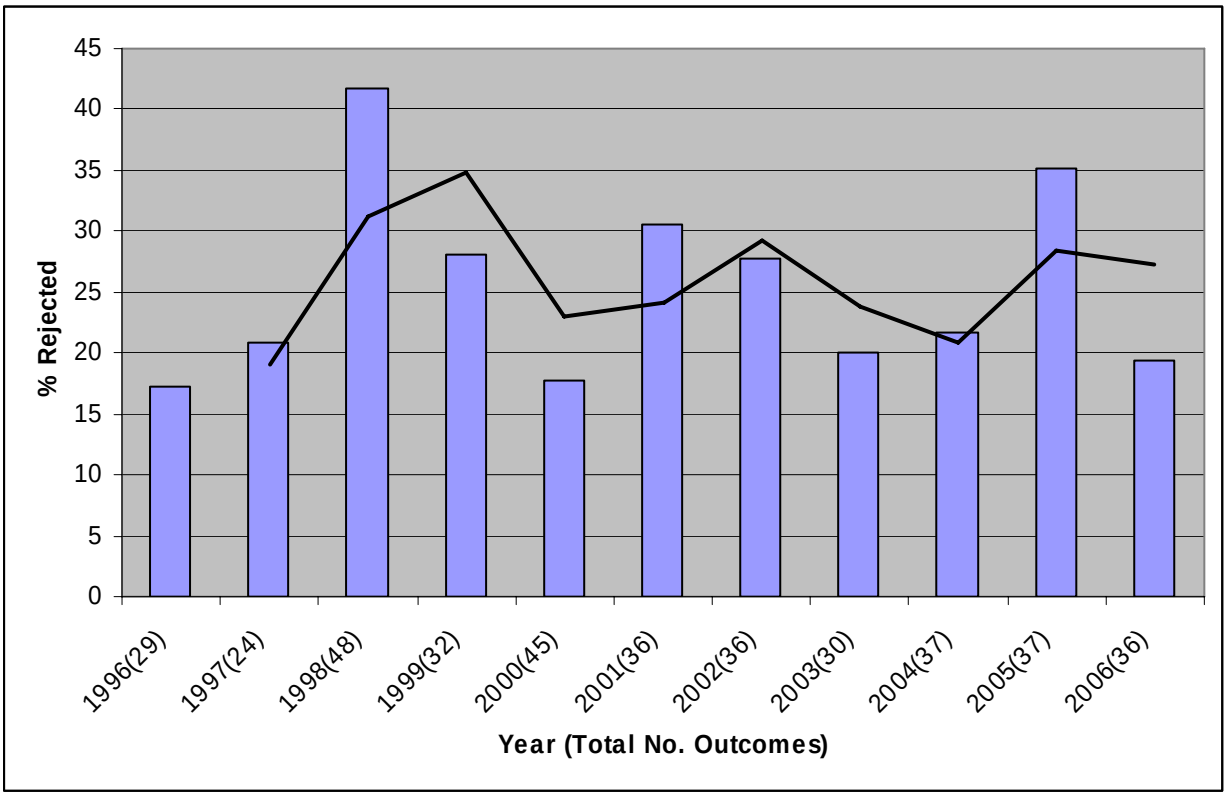


Table. 1: ATC code classification

A Alimentary tract and metabolism
B Blood and blood forming organs
C Cardiovascular system
D Dermatologicals
G Genito-urinary system and sex hormones
H Systemic hormonal preparations, excluding sex hormones and insulins
J Anti-infectives for systemic use
L Antineoplastic and immunomodulating agents
M Musculo-skeletal system
N Nervous system
P Antiparasitic products, insecticides and repellents
Q Veterinary drug
R Respiratory system
S Sensory organs
V Various

Fig. 3: Frequency of rejected applications by calendar year and trend line with frequency of rejection for the previous 2 years



Outcomes of Marketing Authorization applications for Orphan designated medicinal products

Table 4 shows that there were nine orphan designated drugs that were approved in this period. The proportion of orphan designated drugs is actually reaching its highest peak in this years' review (35%; see also table 1). Most orphan drugs have historically been approved in the areas of cancer/immunodulation and metabolism. This still holds true and Nexavar and Sutent are examples discussed above. This year, as mentioned above there are also two neurological orphan medicinal products, both indicated for epilepsy in children (see table 1).

Table 4: Approved MAAs by orphan status of all approved MAAs – by start year

	2000	**2001**	**2002**	**2003**	**2004**	**2005**
Orphan Drugs	2/26 (8%)	7/32 (22%)	7/21 (33%)	4/28 (14%)	4/32 (13%)	9/26 (35%)

Table 5 shows that only one orphan drug had a negative opinion in this last period. This was the application for Mycograb, a product intended for invasive candidiasis. In the view of the Committee, concerns remained over the quality and safety of this product. Overall, 20 (37%) out of 54 orphan designated products have been rejected (negative opinions or withdrawals).[1]

Although there is a trend for a somewhat higher rejection rate in applications for orphan medicinal products as compared with non-orphans (26% as discussed above), this does not appear statistically significant as analysed in the section above on multivariate analysis.

[1] Two products started their reviews in 2006 with outcomes in 2006 and are not in table 5.

Table 5: Proportion of Negative outcomes by orphan status – by start year

	2000	2001	2002	2003	2004	2005
Orphan Drugs	0/12	5/12 (42%)	5/8 (62%)	3/7 (42%)	5/9 (55%)	1/10 (10%)

1.4. Impact of Scientific Advice/Protocol assistance on Marketing Authorisation Applications.

Proportion of MAAs with Scientific Advice (includes protocol assistance)

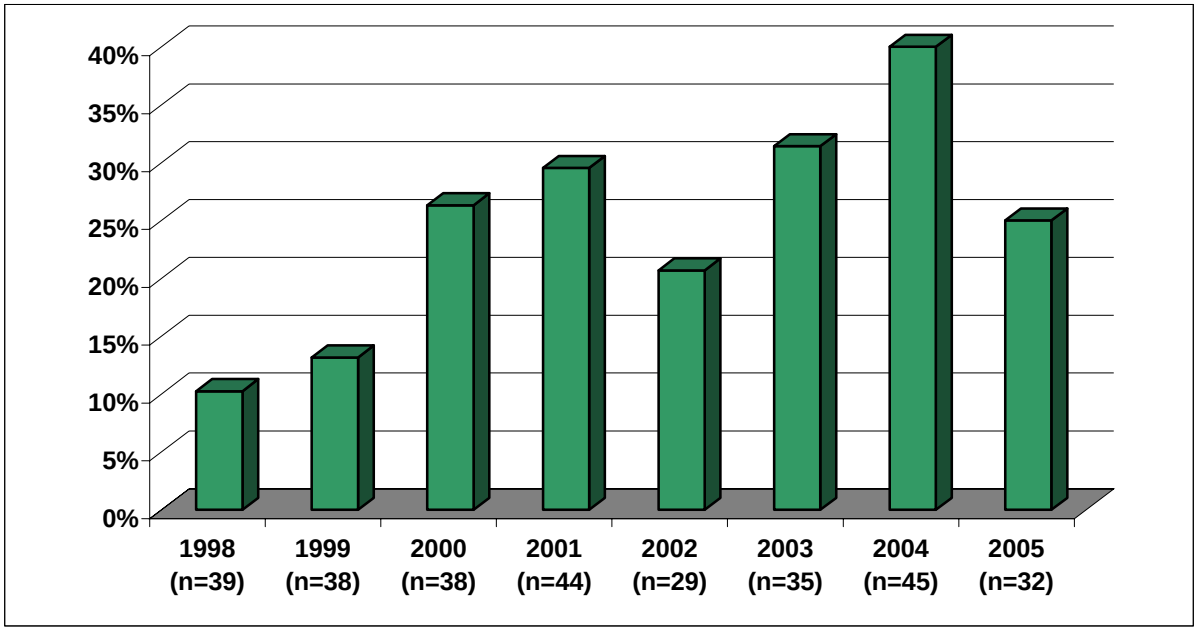
The proportion of MAAs preceded by SA is 25% and pertained to eight of the thirty-two applications submitted in 2005 (Figure 4). Six (23%) (table 1) of the 26 positive outcomes were preceded by scientific advice and two (table 3) out of the six negative outcomes had prior scientific advice.

Included in these figures are 4 (40%) out of the 10 orphan designated products that had protocol assistance before the marketing authorisation application (tables 1 and 3). Altogether there have been fifteen (28%) protocol assistances given to the fifty-four orphan designated products that have reached an outcome in the CHMP review. Protocol assistance was given to eleven (32%) of the thirty-four orphan designated products that had a positive opinion and four (20%) of the twenty with a negative outcome.

We have previously reported that there is an association between prior scientific advice and success of MAAs. Of the two hundred and thirty-six applications with an outcome that have been submitted since 2001 and reached an outcome, the probability of a negative outcome (negative opinion or withdrawal) was 19% (13/68) for applications with CHMP scientific advice compared to 28% (47/168) for application without scientific advice.

It should be noted that state of the art may have changed since scientific advice was sought which could impact on drug development as well as the views taken by the Committee. The applicant is not obliged neither to seek nor to follow the scientific advice that may have been sought several years prior to the actual marketing authorisation application.

Fig. 4 Proportion of MAAs that received SA – by start year



Major objections

Figures 5 to 7 illustrate the incidence of some major objections made by the CHMP after the first review of the MAA (Day 120 List of Questions). These pertain to important aspects of the clinical development such as the choice of study design, the choice of endpoints and effect size. These objections are further subdivided by whether they received scientific advice or not. There are no clear trends. One could expect that these major objections would be less for those products where the applicant had previously sought scientific advice. However, it should be kept in mind that applicants often ask for scientific advice when they wish to deviate from current guidelines and do not always follow the advice given. So although these graphs do not appear to indicate any clear trends, the actual numbers of major objections (efficacy and safety) appear to be less when SA was given (table 6).

Figures 5-7 Incidence of some Major Objections (with or without SA) by start date, from 1998

Fig. 5

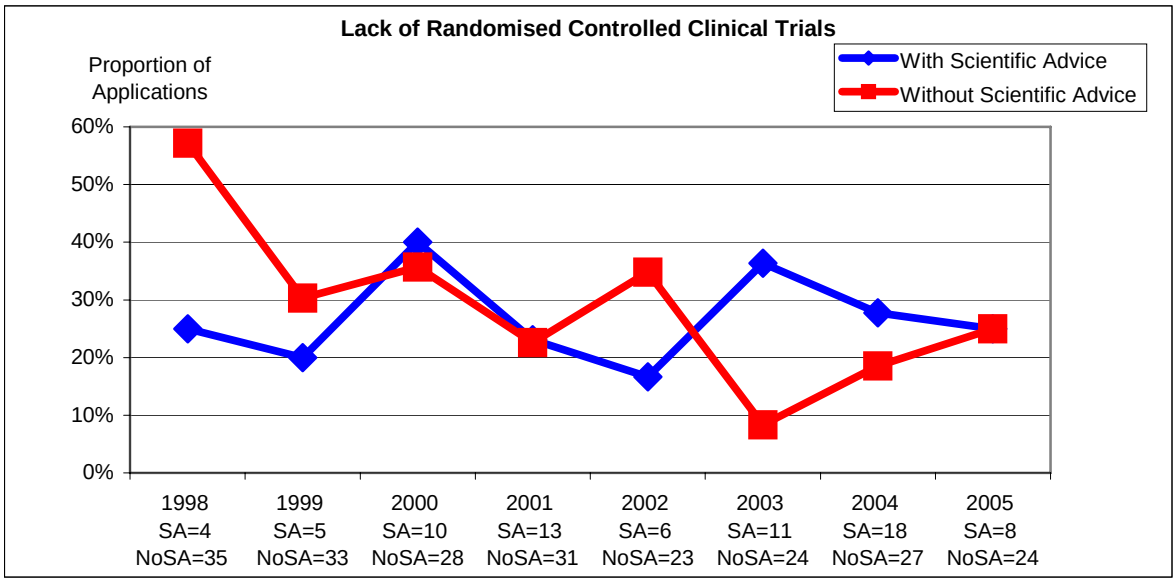


Fig. 6

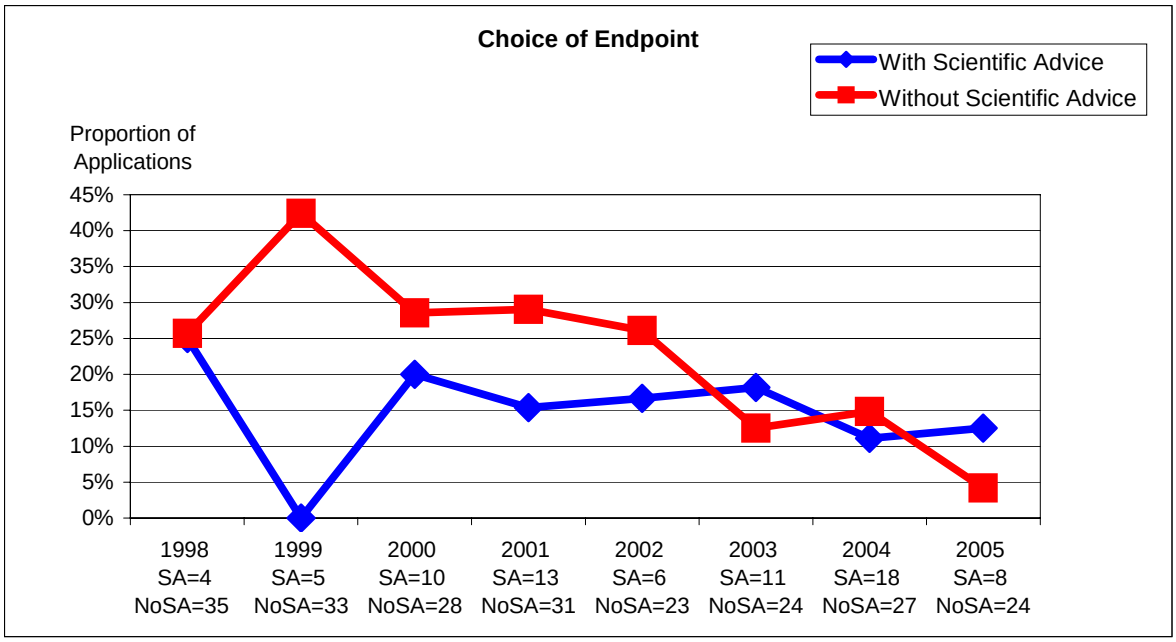


Fig. 7

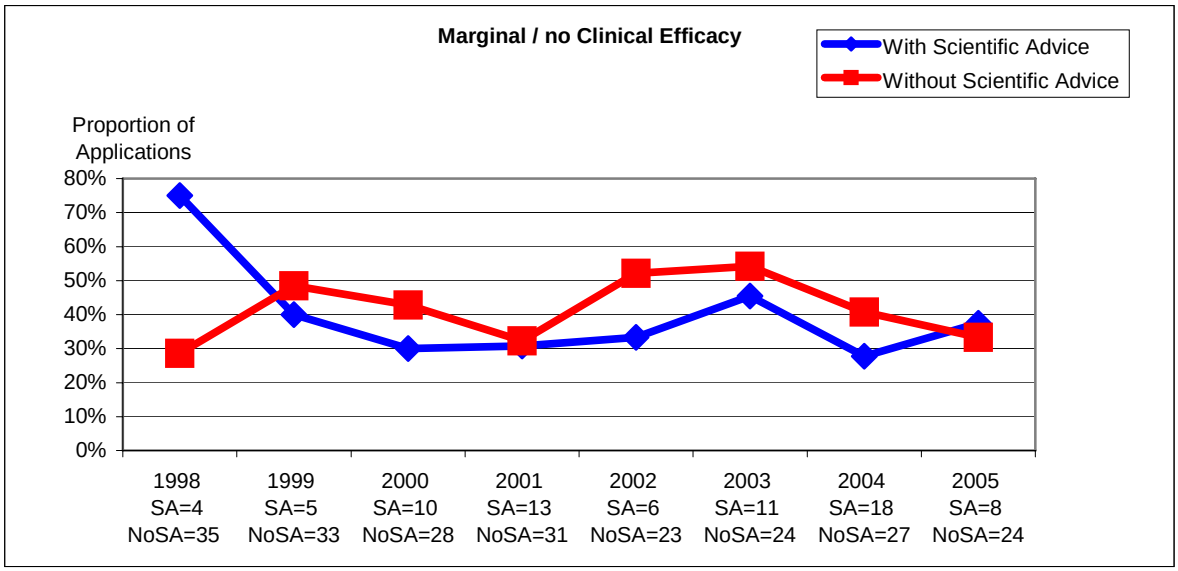


Table 6 : Major Objections (by start year, from 1998)

	SA (N=75)	No SA (N=225)
Average Nr of objections in clinical efficacy	2.30	3.16
Average Nr of objections in clinical safety	0.86	1.15

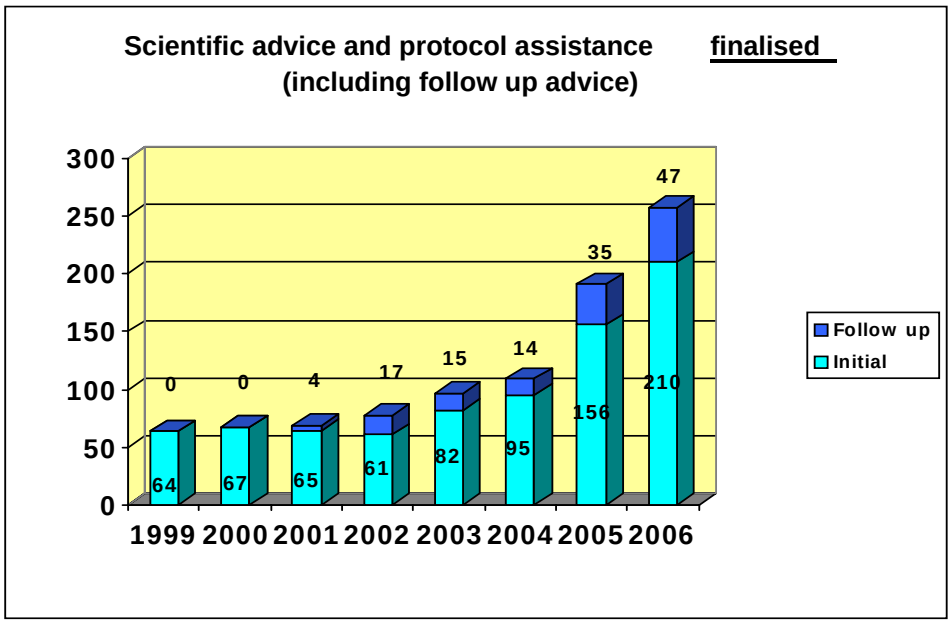
2. Applications for CHMP Scientific Advice/Protocol Assistance

The numbers of SA applications continued to increase markedly and during the October 2006 CHMP meeting the 1000th SA was adopted (Fig. 8). During this year the SA procedure underwent important improvements based on the new Regulation (EC) No 726/2004 which allowed for a new Framework for Scientific Advice (SA) and Protocol Assistance (PA) (EMEA/267187/2005/Rev.1). Following intense internal work and extensive (public) consultation the Framework was published on the EMEA website on 26 April 2006 and implemented as of July 2006.

- To face the increasing workload and the new legal requirements, the SAWP has been extended from 22 members to 26 members and the duration of meetings has increased from 2 to 3 days including increasing the number of slots for discussion meetings with companies.
- The procedure has been streamlined to allow finalisation within 40 or maximally 70 days (compared to the previous 100 day-procedure).
- Broader and more general advice for specific types of medicinal products or treatments, in collaboration with the relevant Working Parties is now accepted (1 request processed so far).
- SA requests on acceptability of the development programme for conditional marketing authorisation (12 requests in 2006) and the development programme for marketing authorisation application under exceptional circumstances (2 requests in 2006) are also being handled.
- Emphasis is also put on the procedure being the result of the collegial work by the coordinators, the experts and the different Working Parties or Scientific Advisory Groups, the COMP and the CHMP, reaching together a common position for formal adoption. Networking is therefore an essential and vital part of the new procedure and formal links with Woking Parties have been established in order to maximise the use of available expertise. **Figure 9** shows the involvement of experts per procedure.
- The definition of the follow-up procedure has been widened to encourage applicants to seek SA or PA as many times as necessary, throughout their development programme. Applicants are now

able to seek a follow-up request on issues not initially included in the first application if they are related to the same therapeutic indication.

Figure 8



The new framework also provides for "Workshops and think-tank meetings on specific and rapidly evolving topics to be organised by the EMEA, involving regulators, pharmaceutical companies, academia/learned societies and patients' representatives, to share "non-confidential knowledge". After a very successful first workshop with academia on biomarkers in clinical development in December 2005, a second workshop on this issue was held at the Agency in December 2006 with academia and this time also with representatives from the European pharmaceutical industry (EMEA/EFPIA workshop).

3. Applications for Orphan status

3.1 Number reviewed and adherence to regulatory timelines

Table 7 shows the number of applied and approved designations for orphan medicinal products, which for the third consecutive year exceeded 100. Two negative opinions were adopted in 2006. The average time to COMP opinion and Commission decision was 57 and 25 days, respectively. Last year the figures were 60 and 50 days, respectively.

As indicated in figure 9, oncology/immunology make up about 50% of all opinions this year. Half of the designated products are potentially for paediatric use (Figure 10). Both these figures are similar to the figures generated in last year's report.

Table 7: Number of products that have received orphan designation 2005 and 2006.

Orphan Medicinal Product Procedures	**2005**	**2006**
Applications for orphan medicinal product designation	118	104
Withdrawals	30	20
COMP opinions (positive)	88	81
Designation EC Decision	88	80

Figure 10: Therapeutic areas for positive COMP opinions in 2006

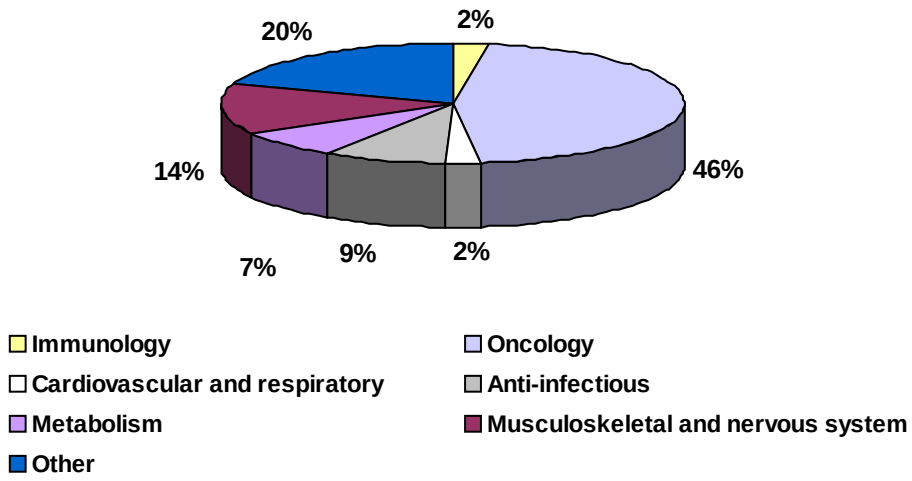
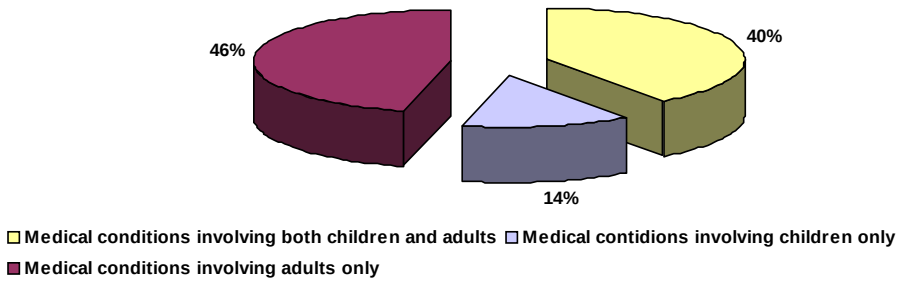


Figure 11: Orphan medicinal products for the treatment of adults and children 2006



II POST-AUTHORISATION ACTIVITIES

The data analysis in this section encompasses scientific Post-authorisation procedures finalised in 2006. A brief overview of the 2006 output compared to 2005 is first provided. Thereafter, a detailed analysis of extensions of indications applications finalised over the period from June 2005 to September 2006 is presented.

1. Scientific Post-authorisation procedures: overview of 2006 output

The year 2006 was marked by a sharp increase in the number of Type II variations (+35%), the two third of which relating to clinical or pre-clinical changes to the Marketing Authorisation. The number of Type I variations increased as well but to a lesser extent (+9%). The number of Follow-up Measures (FUMs) and Specific Obligations (SOs) assessed in 2006 showed a major increase compared to 2005 (+55%). Eighty percent of the FUMs and SOs related to clinical issues, as opposed to 20% to quality ones. The number of Renewals, Annual Re-assessments showed a slower progression, whilst the number of PSURs decreased slightly (see tableVIII).

More details are provided in the EMEA Annual Report 2006 on the activities relating to Variations procedures, FUMs/SOs and PSURs in 2006.

Table VIII. Scientific Post-authorisation procedures: Output 2006 vs. 2005

Procedure	2005	2006	2006 vs. 2005
Type II variations	505	681	+ 35%
Type I variations	628	684	+ 9%
Line extensions	15	15	=
Renewals	40	44	+ 11%
Annual Re-assessments	20	22	+ 11%
FUMs/SOs	1150	1787	+ 55%
PSURs	279	273	- 2%

2. Detailed review of Extensions of indications

The review period considered is from June 2005 to September 2006. This corresponds to the review period used to report on extensions of indications related activities during the EFPIA Info Day held at the EMEA on 5th February 2007.

Forty-eight (48) opinions were adopted for extensions of indications applications over the 15 months considered. These correspond to 39 CHMP assessments, as there were 9 duplicates amongst the opinions. Duplicates were not taken into account in the various analysis performed and presented thereafter. The first objective of this exercise was to look at the processing time of the applications and the factors that may affect it. In addition, the EMEA reviewed the outcome of the questionnaires filled in by the (Co-)Rapporteurs in relation to the quality of the applications for extensions of indications assessed.

A similar exercise was conducted last year, reviewing extensions of indications that received an opinion between June 2004 and May 2005. This analysis was also shared with Industry during the EFPIA Info Day held in 2006. For this reason, an attempt is made to compare the results obtained over the period June 05 – September 06 with those from the previous exercise (June 04 – May 05).

2.1. Involvement of the Co-Rapporteur

The Co-Rapporteur was involved in the assessment for 95 % (37/39) of the extensions of indications finalised between June 05 and September 06. This is a sharp increased compared to last year's review (+ 16%).

2.2. Review times

The overall processing time encompasses the active review time and the clock-stop time. The distribution of the overall processing time for the 39 dossiers is illustrated in figure 12. The mean time was of 197 days 95CI (178;217) and the median time of 188 days 95CI (174;216). Values ranged from a minimum of 60 days to a maximum of 377 days. The shortest time corresponds to the expedited review of Herceptin in the indication of early-stage treatment of positive HER-2 breast cancer. Similar types of submissions in important oncology indications have exceptionally been dealt with by the Agency in an expedited manner in the past. The two procedures that were reviewed in more than 300 days also had the two largest clock-stop times.

The distribution of the active review times is illustrated in figure 13. The mean time was of 151 days 95CI (142;161) and the median time was of 148 days 95CI (139;159). Values ranged from 60 to 227 days. The active time corresponding to the first phase of the assessment (from starting date to adoption of opinion or 1st Request for Supplementary Information) remained within the stipulated 90 days.

The distribution of the clock-stop time for the various dossiers considered is represented in figure 14. The mean clock-stop time was of 48 days 95CI (36;60) and the median time of 37 days 95CI (27;53). Values ranged from 12 to 184 days. Only three procedures had a clock-stop exceeding 100 days.

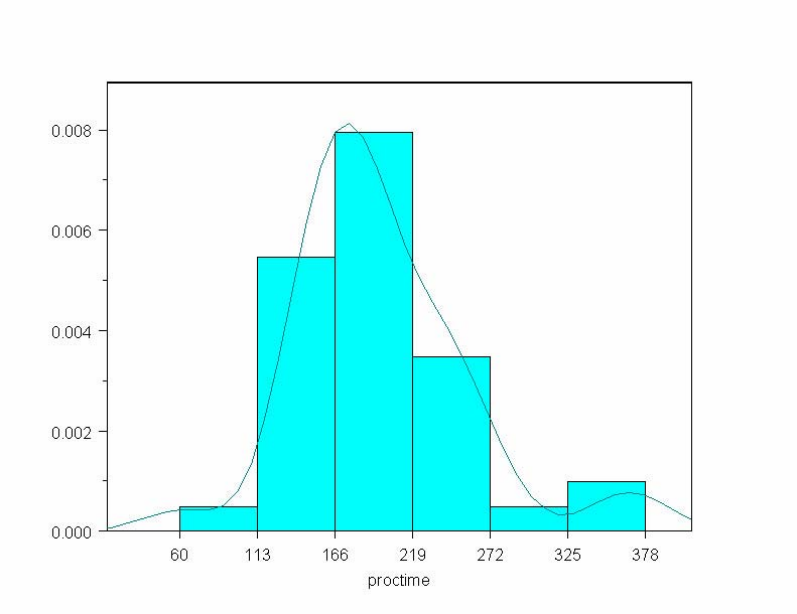


Figure 12. Histogram of the distribution of the overall processing times

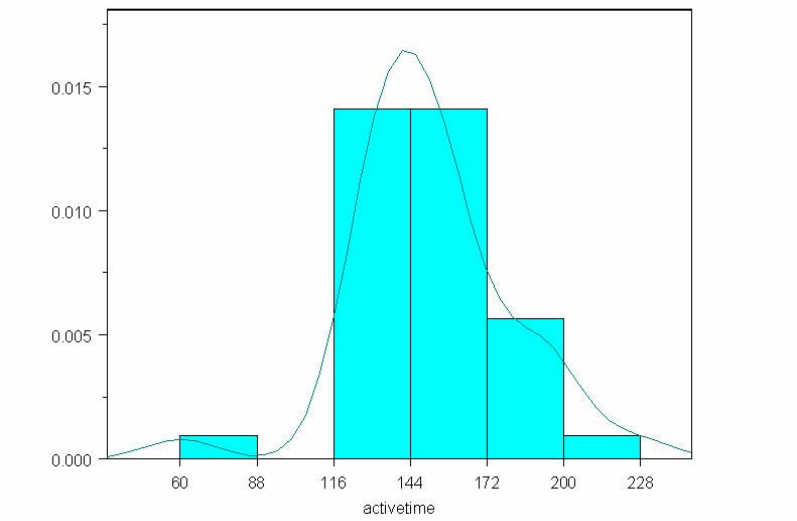


Figure 13. Histogram of the distribution of the active review times

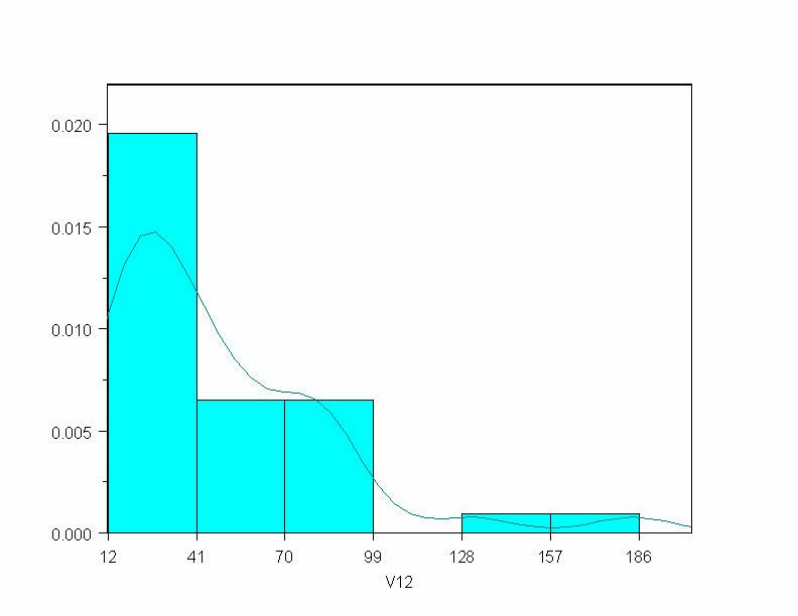


Figure 14. Histogram of the distribution of the clock-stop times

2.3. Request for Supplementary Information (RSIs)

At least one RSI was adopted for all the procedures but one. In addition, the period reviewed indicates a sharp increase in the number of RSIs per procedure compared to last year's analysis (figure 15). The two thirds of RSIs related to both efficacy and safety issues, whilst 20% related to efficacy matters only and about 10% to safety concerns only.

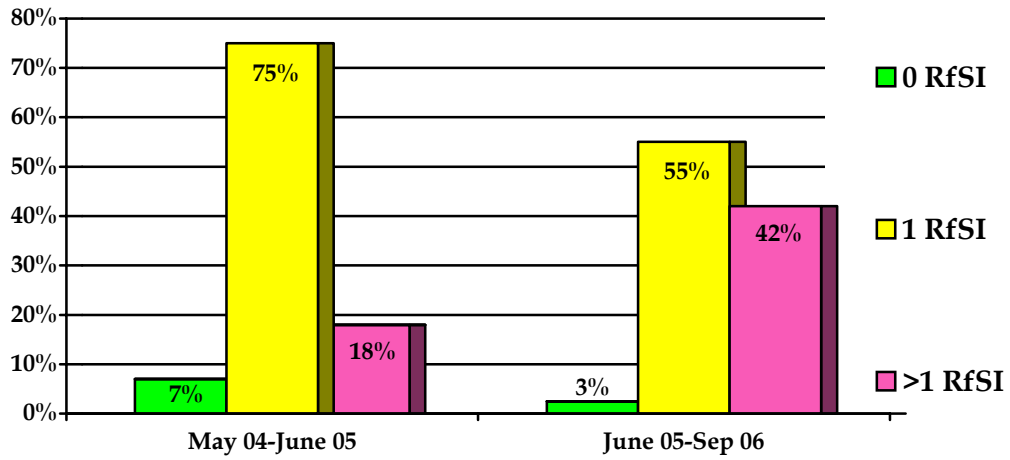


Figure 15. Number of RSIs per procedures

Major Objections were adopted in more than a third of the procedures (14/39). The Major Objections did not significantly increase the mean and median of the overall processing time, active review time, and clock-stop time, as shown in table IX and figures 16 to 18.

Table IX. Mean and median values of the overall processing time, active review time and clock-stop time, with and without Major Objections

	Major Objections N = 14		No Major Objections N = 25		p value*
	Mean (95% CI)	Median (95% CI)	Mean (95% CI)	Median (95% CI)	
Overall time	203 (182;224)	188 (174;267)	194 (167;220)	181 (160;216)	0.704
Active time	154 (143;165)	147 (140;194)	150 (138;162)	149 (138;164)	0.985
Clock-stop time	49 (37;61)	44 (33;82)	45 (29;61)	27 (20;53)	0.725

* The p value corresponds to the comparison of the Kaplan Meier estimates of the survival function (log-rank test)

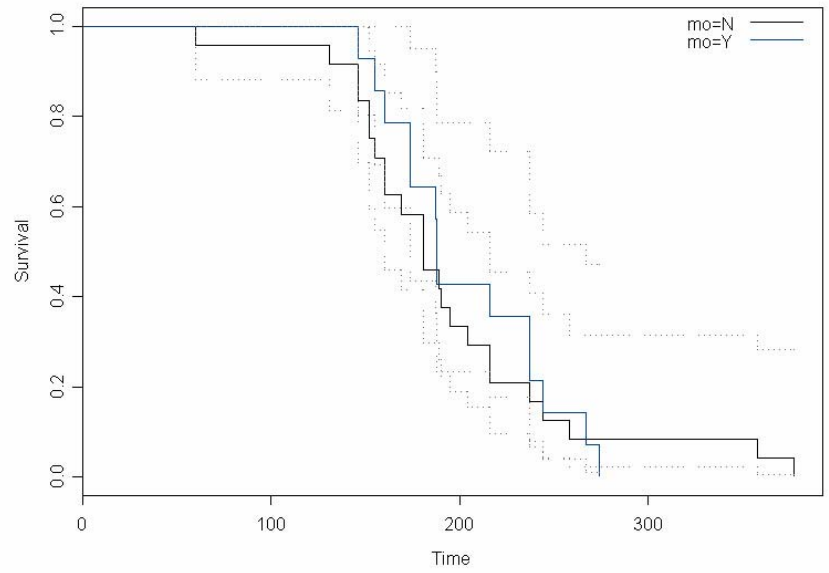


Figure 16. Kaplan Meier estimate of the survival function for the overall processing time with and without Major Objections.

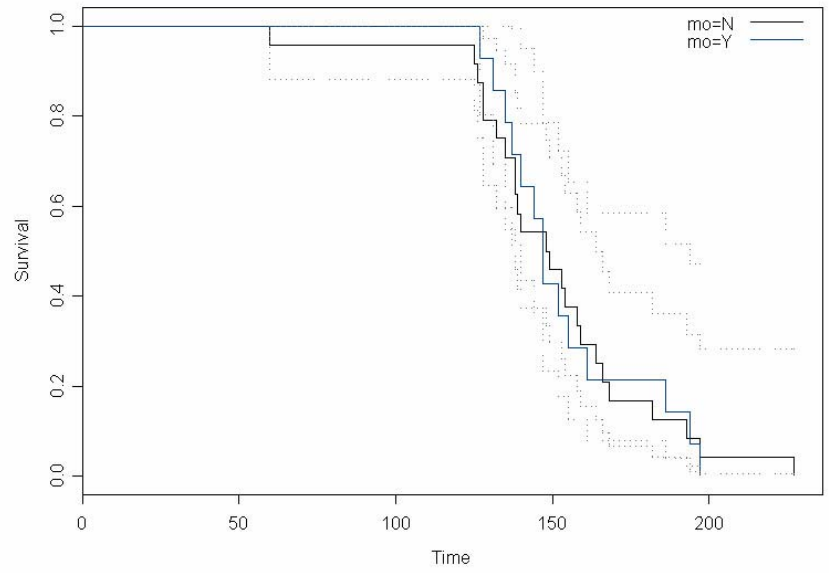


Figure 17. Kaplan Meier estimate of the survival function for the active review time with and without Major Objections.

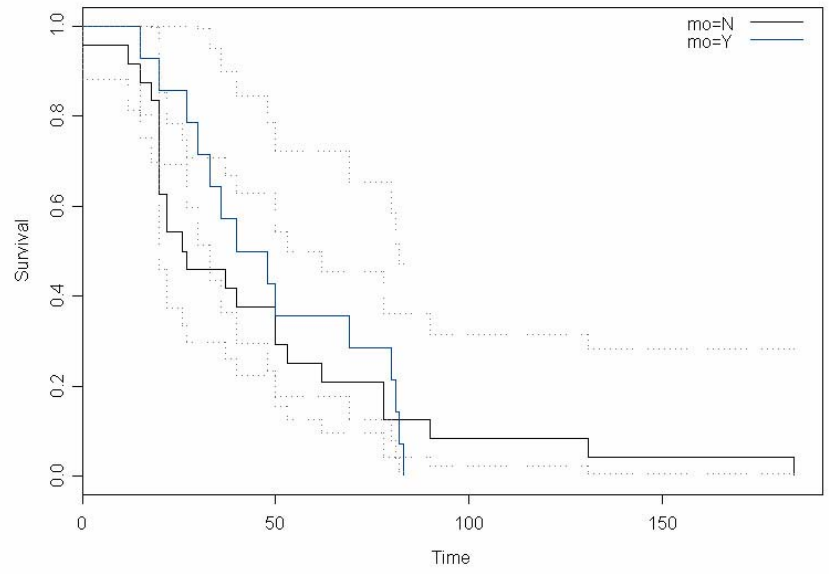


Figure 18. Kaplan Meier estimate of the survival function for the clock-stop time with and without Major Objections.

2.4. Outcome

All the 39 opinions adopted were positive. Four applications were withdrawn before reaching an opinion. Three positive opinions were preceded by an oral explanation and one was granted after re-examination procedure. Seventy four percent (29/39) of procedures were adopted with post-authorisation commitments (64% in 2005). For most of the procedures concerned (14/29), the commitments related to both efficacy and safety concerns.

The majority of the new indications related to medicinal products approved for the treatment of various forms of cancer, including early-stage breast cancer, squamous cell cancer of the head and neck, metastatic gastric adenocarcinoma, cervix carcinoma, follicular lymphoma, dermatofibrosarcoma protuberans, myelodysplastic syndromes, myeloproliferative diseases, and myelodysplastic/myeloproliferative diseases. Several extensions of indication were also granted for the diagnosis or treatment of central-nervous-system disorders (notably advanced Parkinson's disease and epilepsy), of diabetes, and of cardiovascular, infectious, rheumatoid and inflammatory-bowel diseases. The distribution of new indications per ATC code is provided in figure 19.

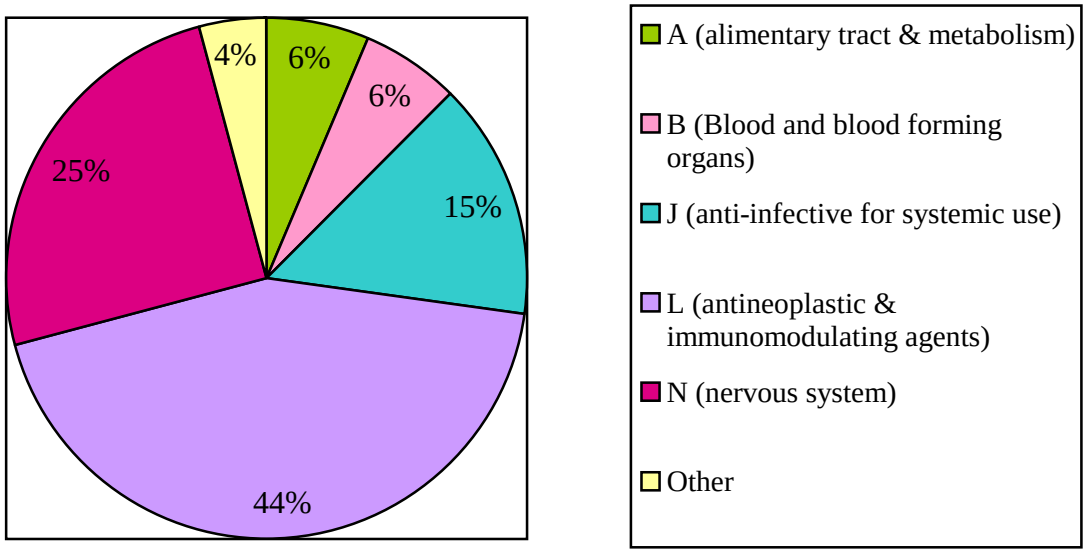


Figure 19. Distribution of Extensions of indications with positive CHMP opinion per ATC code

2.5. Scientific Advise (SA)

A SA was sought prior to submission for 9 of the 39 procedures (20%). This corresponds to a twofold increase compared to the previous review period (11% of procedures finalised between June 04 and May 05 went through the SA procedure).

The small size of the sample studied does not permit to draw robust conclusions on the potential impact of SA on the subsequent outcome of the procedures, or on the concerns raised during the assessment). There was no statistically significant association between prior SA and adoption of Major Objections (Table X) and the SA did not impact on the final outcome, as all the opinions adopted were positive. However, it is noteworthy that none of the four applications withdrawn before opinion were subject to prior SA. Beside, although SA are sought for a new indication, the products concerned have already shown a positive benefit/risk profile in other indications and thus, the situation is not comparable to that of complete new marketing authorisation applications.

Table X. $\chi 2$ test assessing the impact of prior Scientific Advise on subsequent Major Objections

	Major Objections	No Major Objections	Total
SA	3	4	7
No SA	11	20	31
Total	14	24	38

Degrees of freedom: 1; $\alpha = 0.05$
Calculated χ^2 value (0.13) < tabled χ^2 value (3.84)

2.6. (Co-)Rapporteurs's satisfaction with the application dossier

(Co-)Rapporteurs were asked to score three parameters, using a satisfaction scale from 0 to 10.

- Parameter 1: was the dossier presented in a satisfactory way (layout, organisation of data, etc)?
- Parameter 2: were all important data/analysis included in the dossier thereby making benefit risk assessment easy?
- Parameter 3; Was the "scientific overview" (expert report) sufficiently critical?

Feedback was received for 72% of the procedures reviewed (28/39).

For parameter 1, the mean score was 6.5. Values ranged from 2 to 10, and 50% of the dossiers were rated more than the median score 7 (figure 20).

For parameter 2, results were also positive with a mean score of 6.2. Values ranged from 0 to 10, and again 50% of the dossiers were rated more than the median score 7 (figure 21).

The lowest score went to the quality of the clinical overview. Although the mean and median values were 5.4 and 6 respectively, the lack of critical assessment was occasionally reported. Values ranged from 0 to 9 (figure 22).

Four of the 39 dossiers, corresponding to two medicinal products were scored 4 or less for the three parameters.

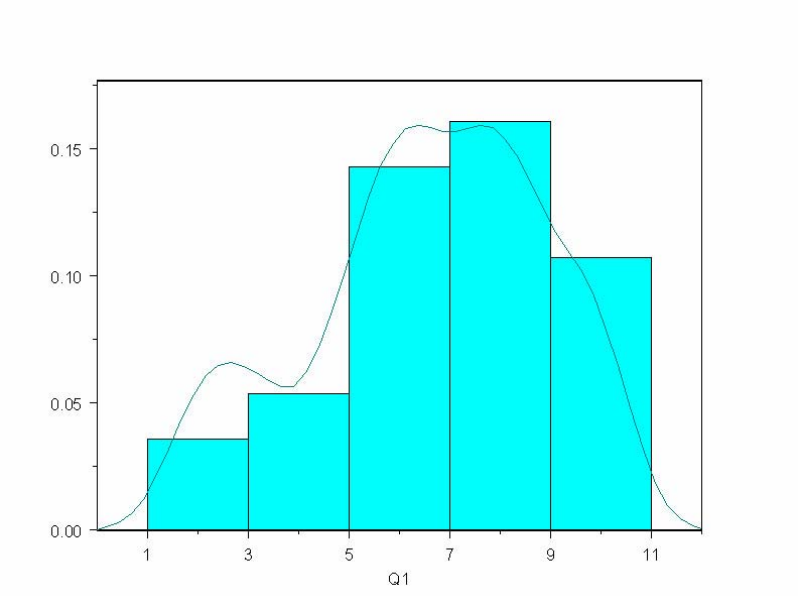


Figure 20. Histogram of the distribution of scores for parameter 1

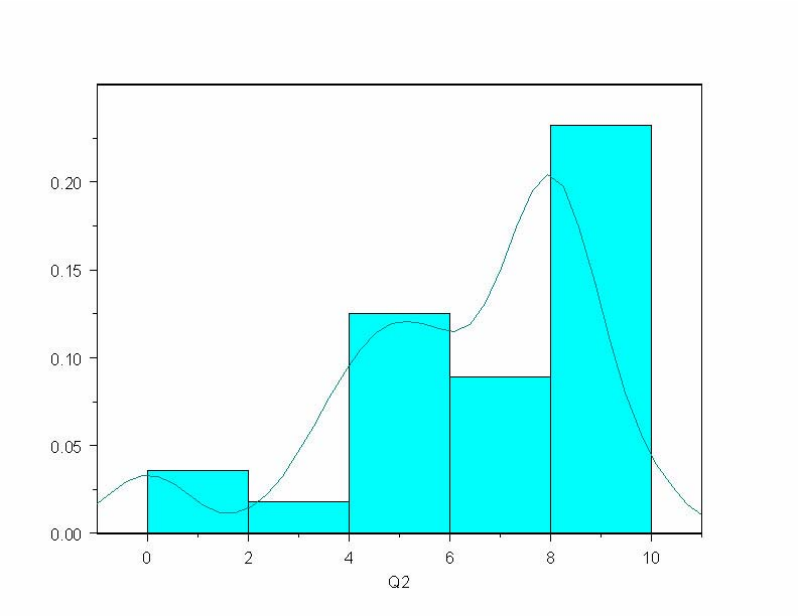


Figure 21. Histogram of the distribution of scores for parameter 2

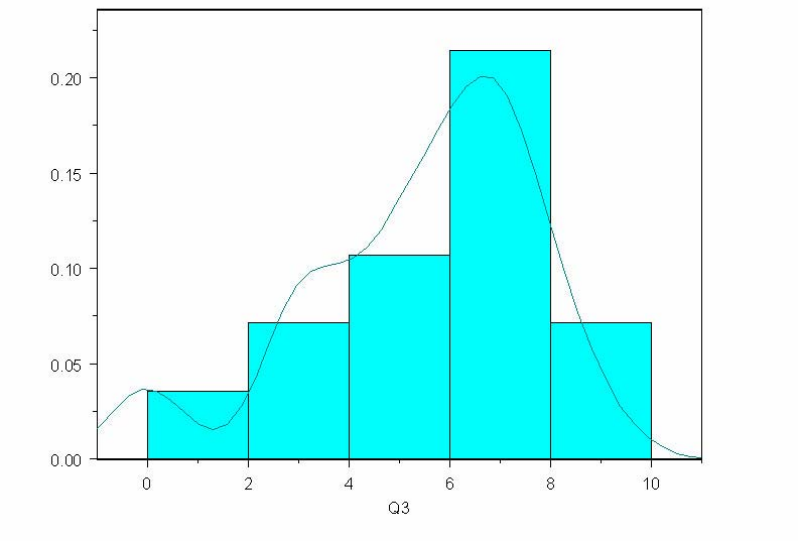


Figure 22. Histogram of the distribution of scores for parameter 2

