The European Agency for the Evaluation of Medicinal Products

15 March 2000
CPMP/602/00

Applications in the Centralised Procedure 1995 to July 1999 - an analysis of outcomes

SUMMARY

One hundred and thirty-five full applications for Marketing Authorisation, submitted to the EMEA during January 1995 to July 1999 attained an outcome in the CPMP scientific evaluation process.

Thirty-eight (28%) of these applications had a negative outcome, i.e. they were either withdrawn or had a negative CPMP opinion. In therapeutic areas such as the antineoplastic, blood and nervous system, the negative outcome rate was 57% (17/30) overall during 1998 to July 1999. Over applications with a negative outcome, methodological concerns over study design, choice of endpoint, comparator and selected population were raised more frequently than over those with a positive CPMP opinion.

Public information available on the FDA homepages indicated that the FDA, by January 2000, had authorised 13 (34%) of the 38 applications that had a negative outcome in the EU centralised procedure. The scientific committee (CPMP) of the EMEA therefore appears to have a different attitude towards data requirements necessary for obtaining a marketing authorisation, *e.g.* requirements for controlled data. However, it should be kept in mind that the US FDA operate with additional tools for drug approval such as rolling INDs and conditional approvals, none of which are available within the EU regulatory framework.

Only 11% of applications received CPMP scientific advice prior to the submission of the application. It is desirable that scientific advice become more utilised by intending applicants. It may then be anticipated that applicants will submit files that better comply with EU requirements and that the rate of negative outcomes in the centralised procedure will be reduced.

In addition, the systematic review of the European drug regulatory system in year 2001 will further influence the regulatory environment.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Switchboard (44-20-7) 418 8400 Fax (44-20-7) 418 8613
E-mail: mail@emea.eudra.org http://www.eudra.org/emea.html

1 INTRODUCTION

Following the establishment of the European Medicines Evaluation Agency (EMEA) and the Centralised procedure, the scientific evaluation of new applications has attracted great interest.

The EMEA makes publicly available the European Public Assessment Report (EPAR) which conveys the main features of the scientific discussions held in its scientific Committee for Proprietary Medicinal Products (CPMP) for applications which have been granted a marketing authorisation. In addition, the scientific grounds for a negative CPMP opinion, which prevents a marketing authorisation, are also published.

A publication on the EMEA website from May 1999 focused on an analysis of applications that were withdrawn by the applicant during the scientific evaluation process to prevent a negative CPMP outcome. In that analysis, the CPMP concerns over efficacy were identified as the ones most relevant for non-approvability. Subsequent to the EMEA analysis of such "withdrawals" from the review process of the centralised procedure, the EMEA has created a database for all new full applications in the centralised procedure. This database constitutes a tool for understanding those factors that may have influenced the outcome of applications in the centralised procedure, whether they were granted a positive opinion by the CPMP or withdrawn from the evaluation process.

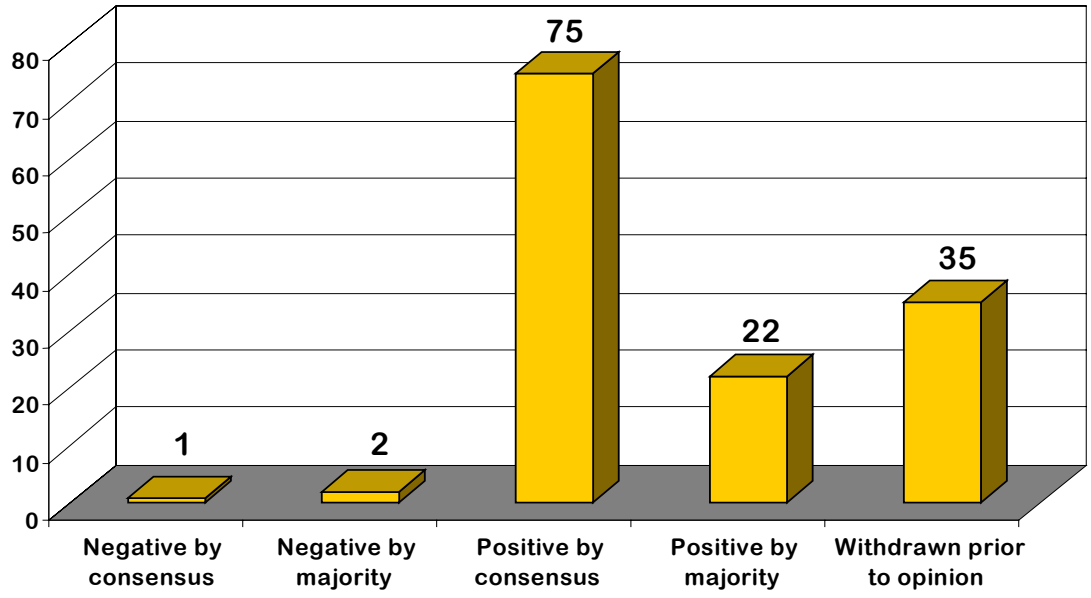
This report describes the various outcomes for centralised applications from January 1995 to July 1999 for these new active substances (excluding double applications). Special focus is on the following aspects: the overall outcome in the CPMP scientific review for 135 full applications from 1995 to July 1999; analysis of applications from 1998 to July 1999 by certain therapeutic areas following categorisation of the CPMP major objections at the time of the List of Questions (day 120 of the procedure); comparison of EU applications with a negative outcome (withdrawn application and negative CPMP opinions) with other regulatory authorities, notably the US FDA.

2 RESULTS

2.1 Overall outcome in the CPMP scientific review for human medicinal products 1995 to 1999

Figure 1

Overall outcome for Centralised procedures 1995 - July 1999 (n = 135)



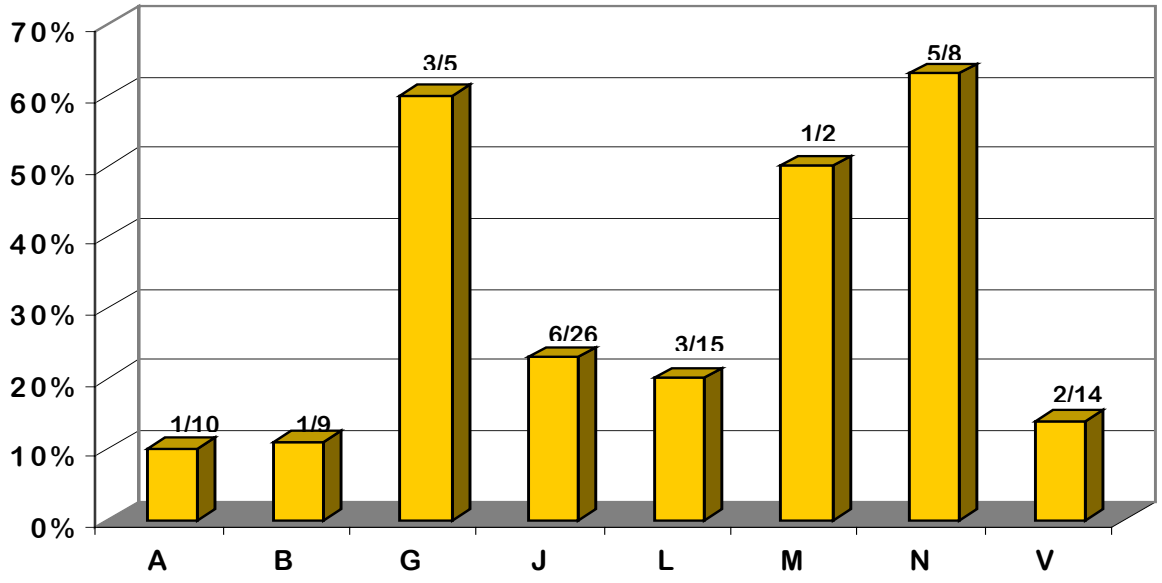
A CPMP positive opinion by consensus is the most common outcome as shown in 75 (56%) applications (figure 1). Thirteen positive opinions were approved under exceptional circumstances. All but one of these were approved by consensus. Figure 1 also demonstrates that 38 (28%) of the 135 applications with an outcome during the 1995 to July 1999 scientific review had to be withdrawn or had a negative CPMP opinion. Twenty-two (16%) positive CPMP opinions were adopted by majority, i.e. that some CPMP members abstained from voting, or had divergent opinions as made public in the EPAR on the individual product. Those divergent opinions were further analysed by ATC code (table 1).

Table 1
ATC codes and related therapeutic areas

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 preparation excl. sex hormones
J	General antiinfectives for systemic use
L	Antineoplastic and immunomodulating agents
M	Musculo-skeletal system
N	Nervous system
P	Antiparasitic products, insecticides and repellents
R	Respiratory system
S	Sensory organs
V	Various

Figure 2

Proportion of divergent positive CPMP opinions (of all positive opinions by ATC code). Centralised procedures 1995 - July 1999



Footnote: One (of 1) divergent opinion was in the dermatological area. There were no positive divergent opinions in ATC codes C, H and S.

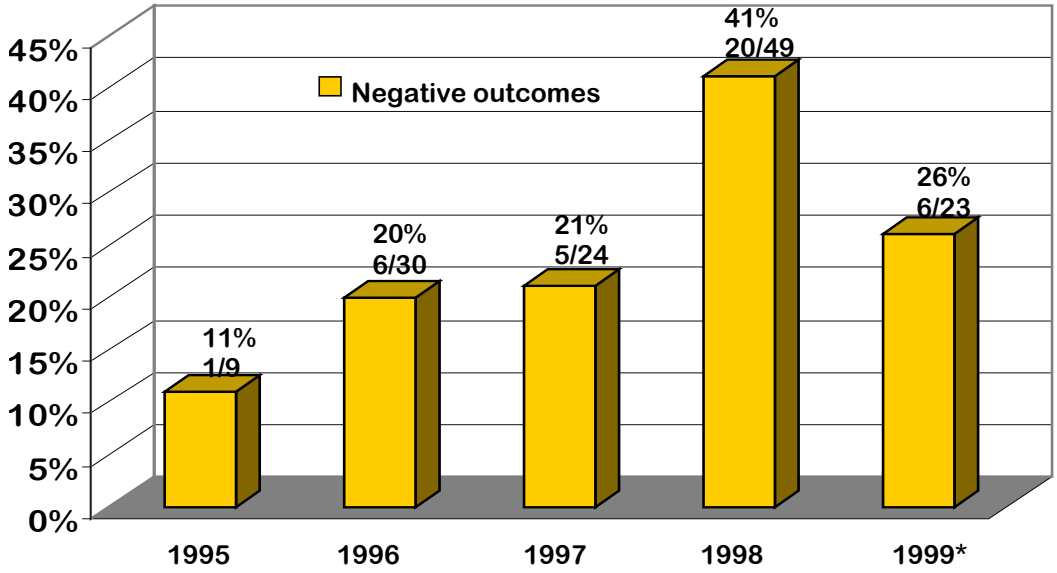
Figure 2 describes the relative occurrence of divergent positive CPMP opinions by the different therapeutic areas during 1995 to July 1999. Notably divergent opinions were particularly frequent in

the nervous system area (5 (63%) divergent opinions of 8 positive opinions), whereas positive consensus views appeared more often in other therapeutic areas.

Overall, the rate of negative outcomes has increased since the start of the centralised procedure as indicated in figure 3. The rate reached a peak in 1998 with 20 (41%) of the 49 applications facing a negative outcome. This peak is explained by the CPMP position not to allow more than a 6 months' clock stop, thus putting pressure on the applicant to submit further data. By July 1999 the rate was 26%, but rose to 34% (11/32) by the end of 1999. The decision to withdraw the application from further evaluation was taken by the applicants after receipt of the List of Questions (day 120) in about one third of the cases, with a further third after receipt of the Joint Assessment Report (day 150), and the last third after the Oral Explanation (day 180 –210 of the evaluation).

Figure 3

Negative outcome rate in the Centralised Procedure from1995 to July 1999



* Refers to data until July 1999

2.2 Analysis by therapeutic areas

The centralised system operates with 2 categories; Part A (Biotechnology/Biologicals) and Part B (New Chemical Entities) products. The outcome rates for these 2 categories are similar (the analysis not presented here).

Figure 4 shows the proportion of negative outcomes by ATC code from 1998 until July 1999.

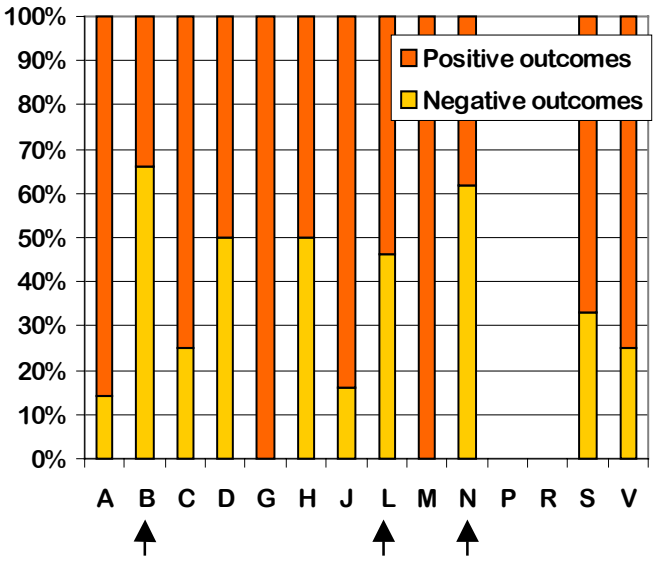
The negative outcome rates are particularly notable in ATC codes B, L and N as indicated by the arrows in the figure. In fact, the negative outcome rate was 57% (17/30) overall for applications in these areas.

Whereas only 30 (42%) out of 72 applications pertain to ATC codes B, L and N, negative outcomes in these 3 therapeutic areas constitute 65% (17 of 26) of all negative outcomes during this period of time.

These 30 applications were further analysed after categorising the major objections raised by the CPMP at the time of the CPMP List of Questions (day 120 of the procedure) in accordance with a predefined set of categories (annex). The results of these analyses are shown in figures 5, 6, 7 and 8.

Figure 4

Proportion of positive and negative outcomes by therapeutic area 1998 to July 1999



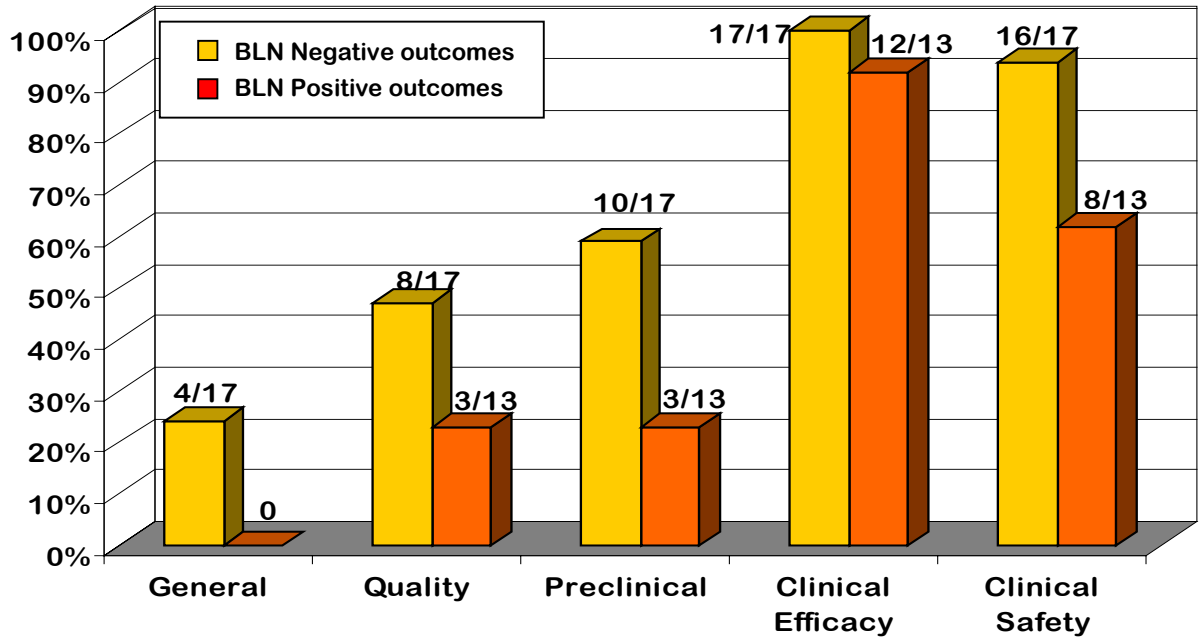
	ATC	Neg. outcome	Pos. outcome	n.
Alimentary	A	1	6	7
Blood	**B**	**6**	**3**	**9**
Cardiovascular	C	1	3	4
Dermatologicals	D	1	1	2
Genito-Urinary	G	0	3	3
System. hormonal	H	1	1	2
Antiinfectives	J	2	10	12
Antineoplastic	**L**	**6**	**7**	**13**
Musculo-skeletal	M	0	1	1
Nervous system	**N**	**5**	**3**	**8**
Antiparasitic	P	0	0	0
Respiratory	R	0	0	0
Sensory	S	1	2	3
Various	V	2	6	8
Total		**26**	**46**	**72**

Figure 5 shows the results of the first level of the analysis highlighting the differences in the proportions of major objections raised by the CPMP between applications with positive and negative outcomes. "General" objections refer to applications which showed numerous major deficiencies in the dossier and could thus be designated as truly "premature" submissions.

Notably, on day 120 (although efficacy concerns are the main reasons for a negative outcome) this "high-level" analysis indicates that CPMP concerns over efficacy were raised just as often for applications with positive outcomes.

Figure 5

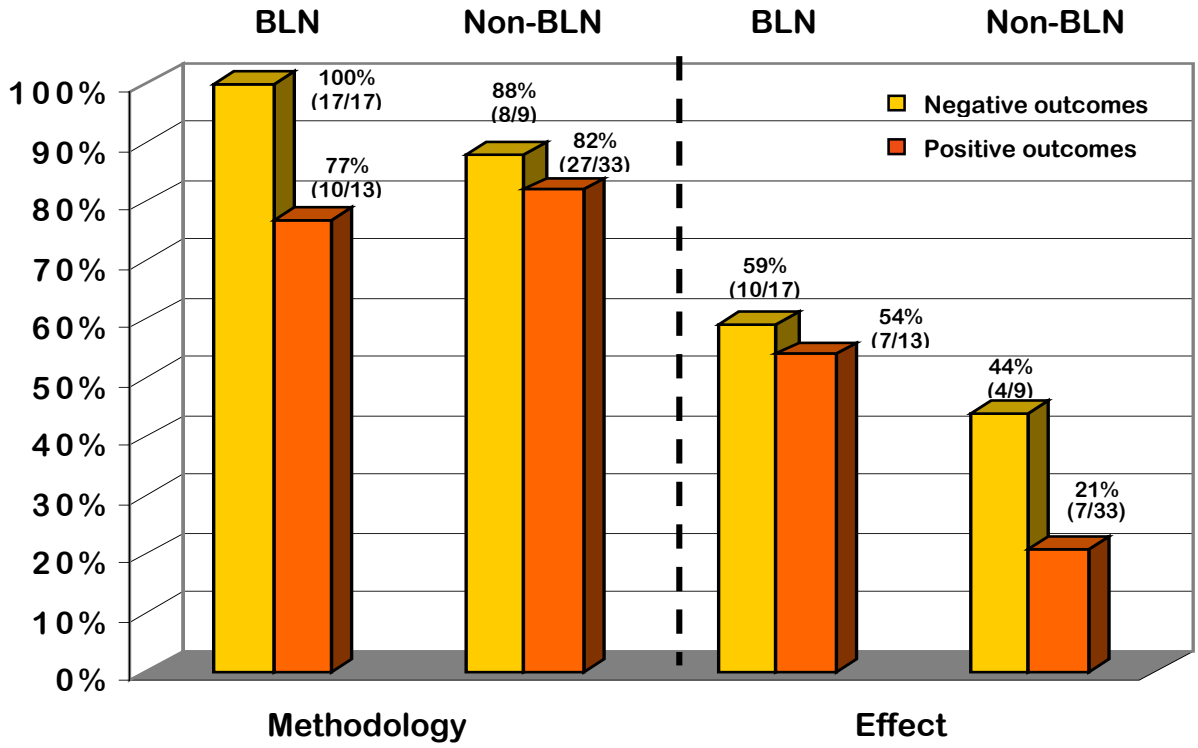
Distribution of major objections for ATC "B, L, N" applications 1998 to July 1999 (n = 30)



To understand the concerns over efficacy, a second and more detailed analysis was performed. The CPMP major objection over efficacy broadly falls into 2 categories relating to methodological concerns and concerns over the magnitude of the clinically relevant effect. CPMP frequently raised concerns over methodological shortcomings and somewhat more often so with respect to applications with a negative outcome than those with a positive outcome (figure 6). With regard to the concerns over the magnitude over the clinically relevant effect, there was no difference between applications with negative and positive outcomes among the B-L-N products (figure 6; 59% vs. 54%). In contrast, for applications in the other therapeutic areas (non-B-L-N products), there seemed to be a difference in the frequency of CPMP concerns raised over the magnitude of the clinical effect between positive and negative outcomes (figure 6; 44% vs. 21%).

Figure 6

Proportions of major objections relating to methodology and clinical effect 1998 to July 1999 (B, L, N products, n = 30, non-B, L, N products = 42)



Methodological concerns raised by the CPMP as major objections at the time of the List of Questions were further analysed at a third level of categorisation (figure 7). Concerns were much more frequently raised over applications with a negative outcome than over those with a positive outcome. Concerns over the study design (mostly lack of controlled data) and the selected population seemed to dominate. The latter often reflects the frequent mismatch between the claimed indication and the population actually studied. As indicated in Annex 1, other efficacy categories have been used in the analysis and the results remain consistent also for these analyses (see below).

Concerns raised over applications with a negative outcome also dominated the safety analysis (figure 8). Mortality concerns were exclusively raised among these applications but also concerns over serious adverse events and lack of interaction studies with safety implications were raised more frequently for products with a negative outcome.

As indicated in figure 8, concerns over the dose justification were quite frequently raised irrespective of a positive or a negative outcome. This is actually also true for the efficacy analysis, where frequent concerns over the dose justification were raised in applications with both positive and negative outcomes. These findings suggest that the decisions taken by the CPMP did not depend on this criterion.

Figure 7

Proportion of major objections relating to clinical efficacy and methodological concerns (B, L, N products, n = 30)

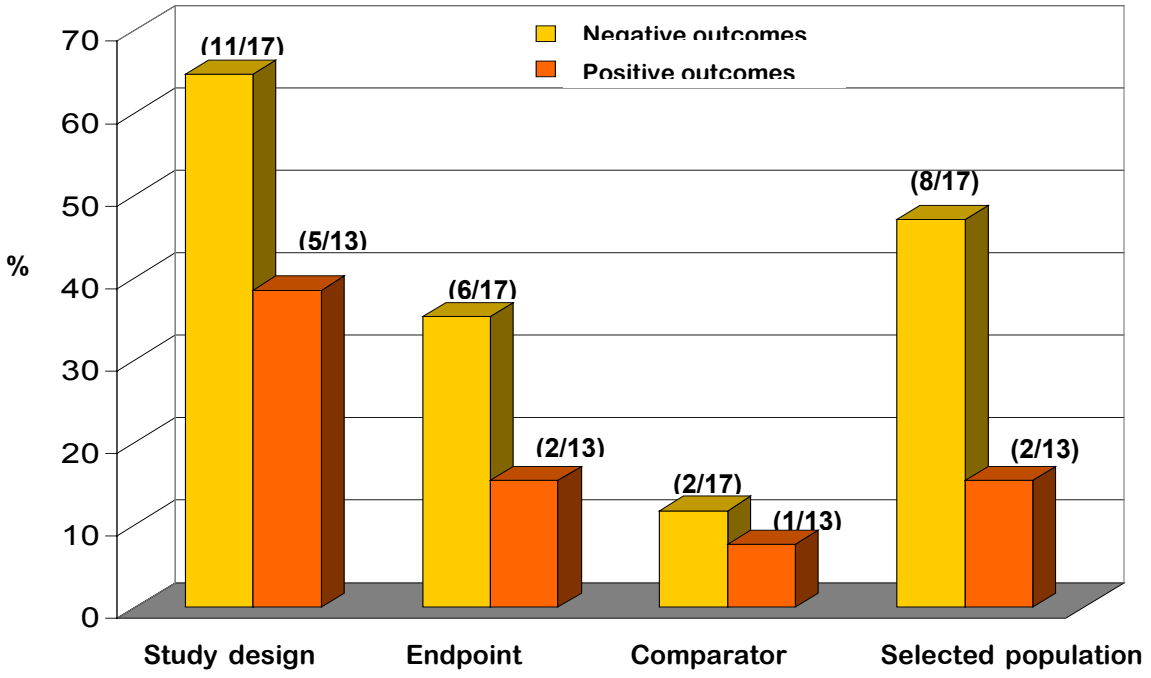
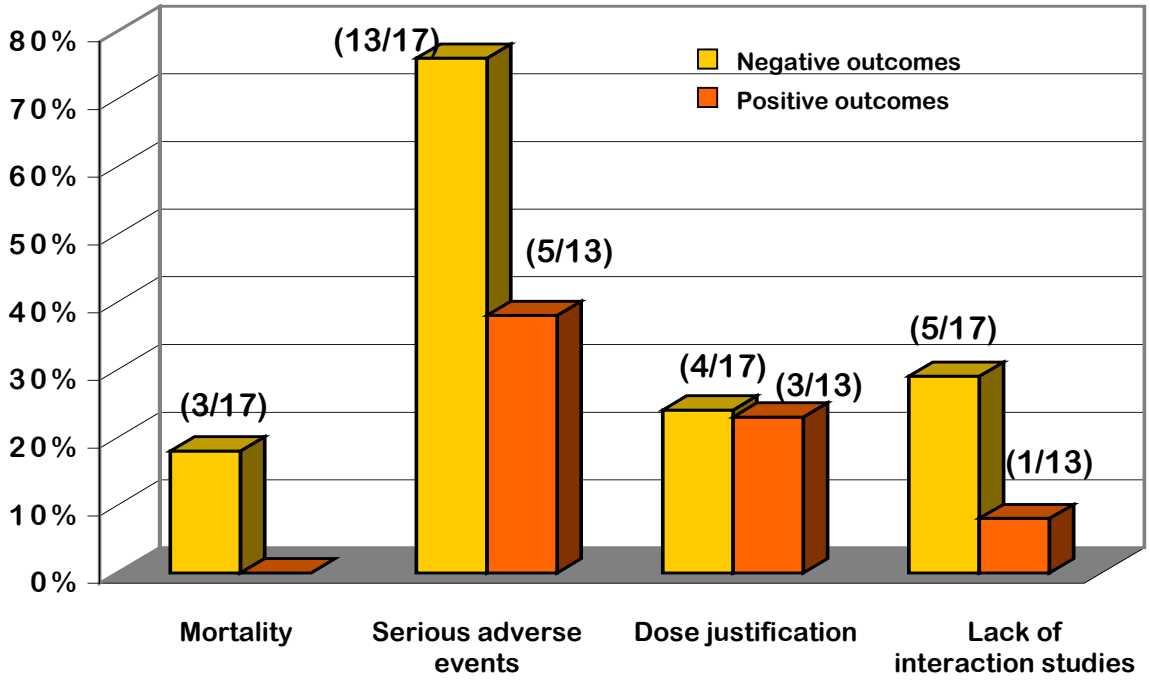


Figure 8

Proportion of major objections relating to clinical safety (B, L, N products, n = 30)



3 DISCUSSION AND CONCLUSIONS

The overall rate of negative outcomes for applications in the European centralised procedure is about 30% and seems to have reached a peak in 1998. In applications with a positive outcome, divergent opinions appeared more frequently in the nervous system area.

For a majority of the 72 applications that reached an outcome between 1998 and July 1999 that were further analysed, the CPMP frequently raised major objections over methodological issues related to efficacy (86%). CPMP major objections over the magnitude of the clinically relevant effect were raised in 38% of these 72 applications.

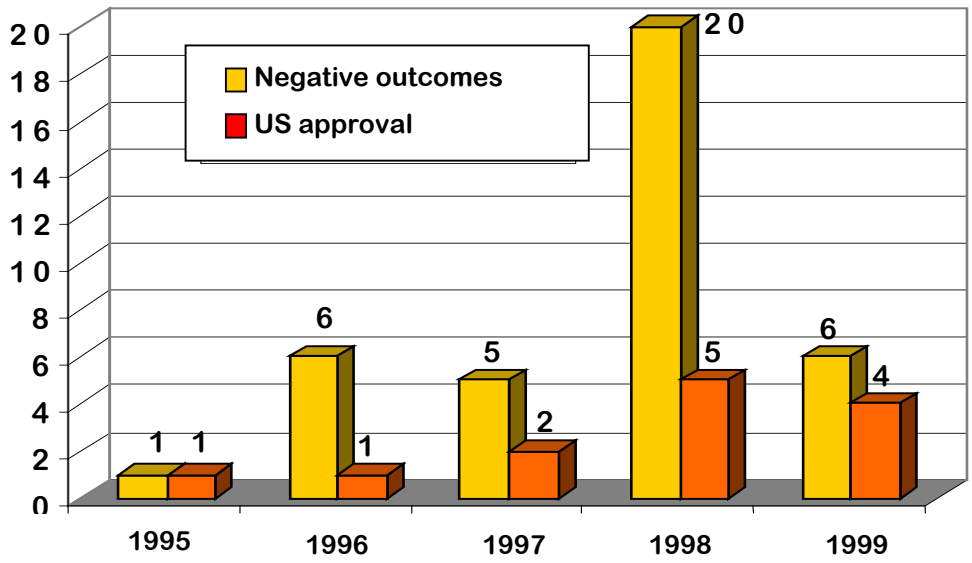
The present analysis is partly focused on applications defined by ATC codes B, L and N where the negative outcome rate was particularly high (57%, 17/30). The numbers contributing to this analysis are relatively small and firm conclusions can not be drawn. However, the CPMP raised methodological concerns (study design, choice of endpoints, selected population, etc) over all these applications. Also concerns over the magnitude of the clinically relevant effect appeared frequently in B-L-N applications irrespective of outcome. In contrast concerns over the magnitude of the clinically relevant effect appeared to be relatively more frequent in non-B-L-N applications with a negative outcome than in those with a positive outcome. Safety concerns such as concerns over serious adverse events and increased mortality were also often raised contributing to a negative benefit/risk balance for many of B, L, N applications.

Further analysis of these applications with negative outcomes in the centralised procedure has been made by comparison with the US system. The US data have been obtained by searching the FDA homepages on the web, for information on approval of a particular INN in the same therapeutic indication. By checking the US licensing status with the European applicant it has been further ensured that the US authorisation corresponded to a similar European application. It should also be pointed out that it is not possible to determine if there are applications that may still (January 2000) be under FDA review, which renders our analysis less complete. The results of these analyses are shown in figures 9 and 10.

Figure 9 indicates the number of EU negative outcomes for a particular year, compared with the number of corresponding US FDA applications up until and including January 2000, irrespective of when the FDA approval occurred. Indeed, there are US approvals for these products that occurred as early as 1985.

Figure 9

Number of applications by year with a negative outcome in the EU centralised system (1995 to July 1999) which are currently (January 2000) authorised in the US

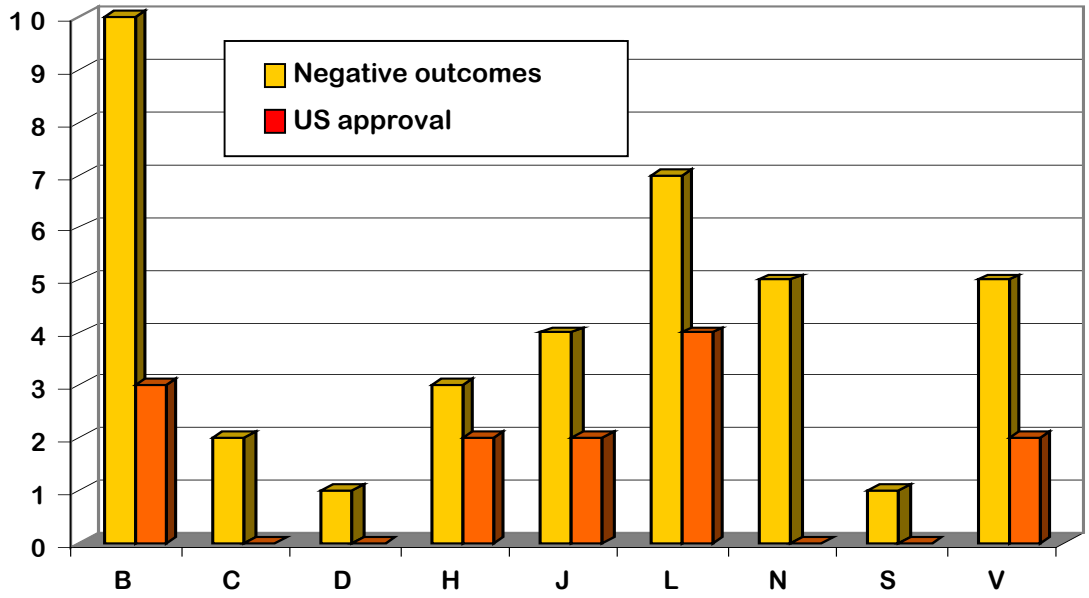


Considering data from 1995 to 1999, the US FDA has approved (on similar indications as applied for in Europe) 13 (34%) of the 38 products which had a negative outcome in the centralised system.

Further analysis relating to the therapeutic areas seems to indicate discrepancies between the two licensing authorities in some therapeutic areas (Figure 10).

Figure 10

Number of applications by ATC code with a negative outcome in the EU centralised system (1995 to July 1999) and currently (January 2000) authorised in the US



The scientific committee (CPMP) of the EMEA appears to have a different attitude towards data requirements necessary for obtaining a marketing authorisation. However, it should be kept in mind that the FDA has for many years been operating with additional tools for drug approvals such as rolling INDs and conditional approvals, none of which are available within the EU regulatory framework. The evaluation does not allow for an analysis of outcomes for individual applications in the two systems. Similar or different review outcomes may therefore pertain to individual applications.

Notably only 11% of applications received CPMP scientific advice prior to the submission of the application. Of the products with a negative outcome during 1998 to July 1999 only 3 received scientific advice. It is desirable that scientific advice become more utilised by intending applicants. It may then be anticipated that applicants will submit files that better comply with EU requirements and that the rate of negative outcomes in the centralised procedure will be reduced. In addition, the systematic review of the European drug regulatory system in year 2001 will further influence the regulatory environment.

Comments should be sent to the EMEA, Evaluation of Medicines for Human Use, attention of Dr. Bo Aronsson.

ANNEX

CATEGORISATION OF CPMP CONCERNS

Area	Main categories	Main concern relating to the major objection
General	• **Major inadequacies**	• Major deficiencies in all/vital parts of the documentation • Other general concerns [to be specified]
Quality	• **Concerns over development**	• Chemical development of the active substance • Pharmaceutical development of the finished product • Biological/Biotech development (e.g. genetics, fermentation, purification) • Batch consistency (e.g. variable manufacturing process) • Transmissible agents (e.g. viruses) • Other concerns over development [to be specified]
	• **Concerns over characterisation**	• Active substance (e.g. biologicals, biotech) • Other concern over characterisation [to be specified]
	• **Concerns over quality control**	• Active substance relating to quality control • Finished product (e.g. control methodology, method validation, specification limits etc.) • Other concerns over quality control [to be specified]
	• **Concerns over stability**	• Active substance relating to stability • Finished product relating to stability • Other concerns over stability [to be specified]
	• **Other quality concerns**	• [to be specified]
Preclinical	• **Concerns over preclinical pharmacology**	• Pharmacodynamics (e.g. study design, data not sufficient to support claimed mechanism or claimed receptor selectivity) • Pharmacokinetics (e.g. insufficient number of animals) • Pharmacokinetic differences to humans having implications for the toxicity studies (e.g. if a major human metabolite is not found in animals) • Other concerns over preclinical pharmacology [to be specified]
	• **Concerns over preclinical toxicology**	• Toxic effects particularly at doses with inadequate safety margin when compared to clinical dose range (dose-dependence, cumulative exposure, reversibility) • Specific tests missing although pharmacodynamics indicate potential toxicity which cannot be traced in the regular battery • Toxicity study design (e.g. limited set of studies not properly justified by the applicant) • Genotoxicity (e.g. in bacteria, in mammalian cells *in vitro* and/or *in vivo*) • Carcinogenicity (e.g. concerns over claimed species-specific mechanisms, concerns over claimed threshold, concerns over carcinogenicity of residual DNA for biopharmaceuticals) • Reproductive performance and developmental toxicity (e.g. concerns over the doses used: not sufficient safety margin to human dose; concerns over study design: missing studies in non-rodents) • Immunological aspects: incomplete information particularly on neutralising antibodies • Other concerns over preclinical toxicology [to be specified]
	• **Other preclinical concerns**	• [to be specified]

Area	Main categories	Main concern relating to the major objection
Clinical Efficacy	• **Methodological concerns (not allowing accurate conclusion on the clinically relevant effect in the applied indication)**	• Study design (e.g. , lack of controlled data) • Analysis/robustness of pivotal data, selection of submitted studies • Choice of endpoint (including rating scales) and validity of the endpoint measurement • Choice of comparator • Selected population (e.g. children or unqualified patients) • Too few patients enrolled • Inadequate duration of treatment • Insufficient long-term follow-up data • Validity of the clinical trial data (e.g. major protocol violations or other GCP issues) • Dose regimen justification relating to clinical efficacy • Lack of specific interaction studies relating to clinical efficacy (including concomitant treatment and neutralising antibodies) • Other methodological concerns not allowing accurate conclusion on the clinically relevant effect [to be specified]
	• **Concerns over the observed magnitude of the clinically relevant effect in the applied indication**	• Marginal/no clinically relevant efficacy (including duration of effect) • Inconsistent data on clinical efficacy • Other concerns over the observed magnitude of the clinically relevant effect [to be specified] • Role in therapy compared to available treatment • Other concerns over the clinically relevant effect [to be specified]
	• **Other clinical efficacy concerns**	• Pharmacodynamics/Pharmacokinetics • Other concerns [to be specified]
Clinical Safety		• Increased mortality • Other serious adverse events • Size/quality/long term data • Severe or lethal clinical interaction • Dose justification relating to clinical safety (e.g. in renal and hepatic impairment) • Lack of specific interaction studies relating to clinical safety (including neutralising antibodies) • Other clinical safety concerns [to be specified]