European Medicines Agency

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Survey 2008 on the performance of EMEA scientific procedures for medicinal products for human use

Executive Summary

Pre-authorisation

2008 saw 70 applications for marketing authorisation reaching an outcome in the CHMP scientific review. This excludes so called duplicate and informed consent applications otherwise bringing the number to 92 applications with an outcome. A higher proportion of products eligible for the centralised procedure via the optional scope and particularly as new active substances were noted this year compared with 2007. The number of generics was about the same as last year but is expected to increase considerably next year. Two applications were approved conditionally this year whereas only 4 started under the accelerated assessment procedure. However, none of these 4 was approved within the stipulated 150 days. 2008 saw a relatively high proportion (33%) with a negative outcome. Particularly orphan medicinal products (56%) and applications from SMEs (58%) appear to have contributed to this. Scientific advice has been given to 55% of all applications prior to commencing the scientific assessment.

Post-authorisation

In 2008, 36 applications (46 with duplicate applications included) for extensions of indications for centrally authorised products had an outcome in the CHMP scientific evaluation. Thirty-one resulted in a final positive opinion, 1 in a final negative opinion, and 4 were withdrawn prior to final CHMP opinion (including 1 during re-examination).
The overall processing time of applications stabilised in 2008. In terms of assessment, almost all applications had at least one request for supplementary information adopted during assessment, and the proportion of procedures with major objections continued to increase in 2008, compared to 2007. Of note, procedures without major objections were processed considerably quicker in 2008 than in 2007, in particular due to shorter clock-stops. Less scientific advisory groups were convened in 2008 than in 2007.

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I. PRE-AUTHORISATION ACTIVITIES

1. Initial Evaluation of Applications for Marketing Authorisation 2008

Introduction

The EMEA Scientific Memory database has been used for these analyses. The data analysed encompasses applications with an outcome up to 31st December 2008 and are entered after an outcome has been reached in the CHMP assessment process. Duplicate applications, i.e. applications which rely on the same dossiers for the same indication have been counted only once. So called "informed consent" applications are also viewed as duplicates in this context.
There have been altogether 92 applications with an outcome during 2008. Excluding the duplicate and informed consent application there were 70 applications with an outcome during 2008 that will be considered in the following paragraphs.

1.1. Adherence to regulatory timelines and review times

Annex 1 describes applications with an outcome in 2008 and their review times; active time and clock-stop. The active time remained within the stipulated 210 days whereas clock-stop times vary greatly with a median of 189 days. The median clock-stop time for applications with a positive outcome was 135 days and 240 days for those with a negative outcome (table 1). Applications with particularly long review times reflect applicants' need for extra long time to respond to the CHMP list of question (LoQ) at Day 120 or at Day 180. In principle, only 3 months is given to respond to the question at Day 120. According to CHMP rules response time can be extended by 3 months (www.emea.europa.eu/pdfs/human/regaffair) given proper justifications. Similarly, an extension by 1 month for the "normal" 1 month allowed for responding to the CHMP questions at Day 180 needs justification. Additional clock stops would not normally be permitted unless relating to issues of inspection (i.e. need for GCP or GMP inspection instigated by the CHMP) or need for additional expert input.
It is noted that applications with SME status (median 250 days) and orphan designation (median 230 days) had particularly long clock-stop times (table 1). For applications with a positive outcome and with particularly long clock-stop times, i.e. > 300 days (Annex 1A) it can be noted that for Mycamine the applicant performed a study in response to a CHMP concern on non-clinical issues, Adenuric had a prolonged clock-stop linked to safety concerns which prompted additional analysis, Latixa had ongoing clinical and non- clinical studies in response to major objections raised by the Committee. For Zevera there were several rounds of questions posed by the Committee related to both efficacy and safety and for Ceplene the Applicant needed time to perform additional clinical analyses on quality of life as requested during the evaluation.
As indicated in the Annex 1B, the CHMP granted extended clock-stops for all applications that eventually failed approval taking the clock stop time up to 672 day for one product application intended for treatment of Myeldysplastic syndrome.

Table 1. Median Clock-stop* times for Applications with an outcome 2008

Type of application	Median time for the clock-stop (days)
All	189
Positive outcome	135
Negative outcome	240
SME status	250
Orphan status	230

* Denotes the accumulated clock-stop time, i.e. both after Day 120 List of Questions and Day 180 List of Outstanding Issues.

1.2. Eligibility and legal basis of Marketing Authorization Applications

Eligibility

Figures 1a and b show eligibility for the products (duplicate applications not included) that had an outcome during 2007 and 2008. Compared with data presented last year there has been a clear increase in the optional scope (56% vs. 37%) applications.

Figure 1a Eligibility* for 59 applications with an outcome 2007.

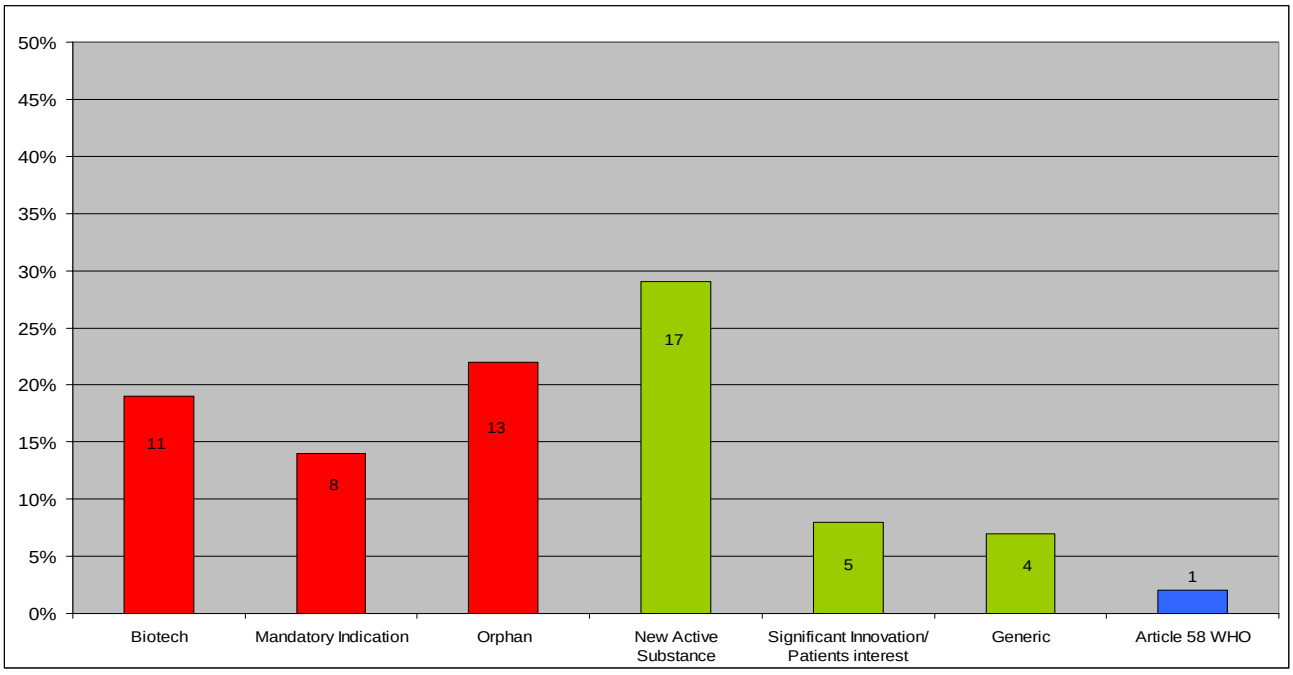
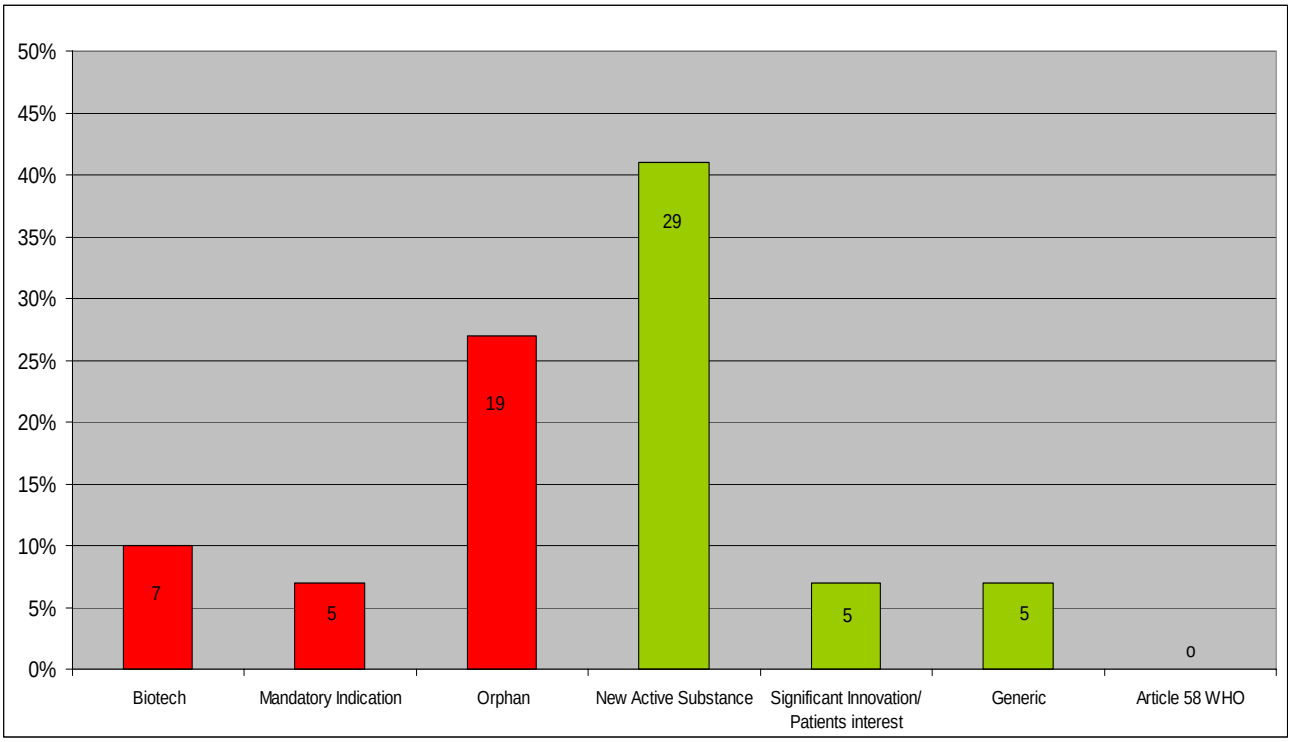


Figure 1 b Eligibility* for 70 applications with an outcome 2008



**Red bars denote the mandatory scope and green bars the optional scope*

** Red denotes mandatory scope and Green optional scope.*

Mandatory scope

Overall the mandatory products make up about 44% (31/70) of all applications with an outcome 2008. That is less than the proportion last year 2007 (63%). Notably there has been an important increase in the number of new active substances from 2007 to 2008 contributing to explaining the relative decrease in the number of products eligible under the mandatory scope (and the relative increase in products eligible under the optional scope). In addition, the number of biotech products and products under the mandatory scope is somewhat less in 2008 than in 2007 whereas the number of orphan medicinal products is in fact higher in 2008 than in 2007.

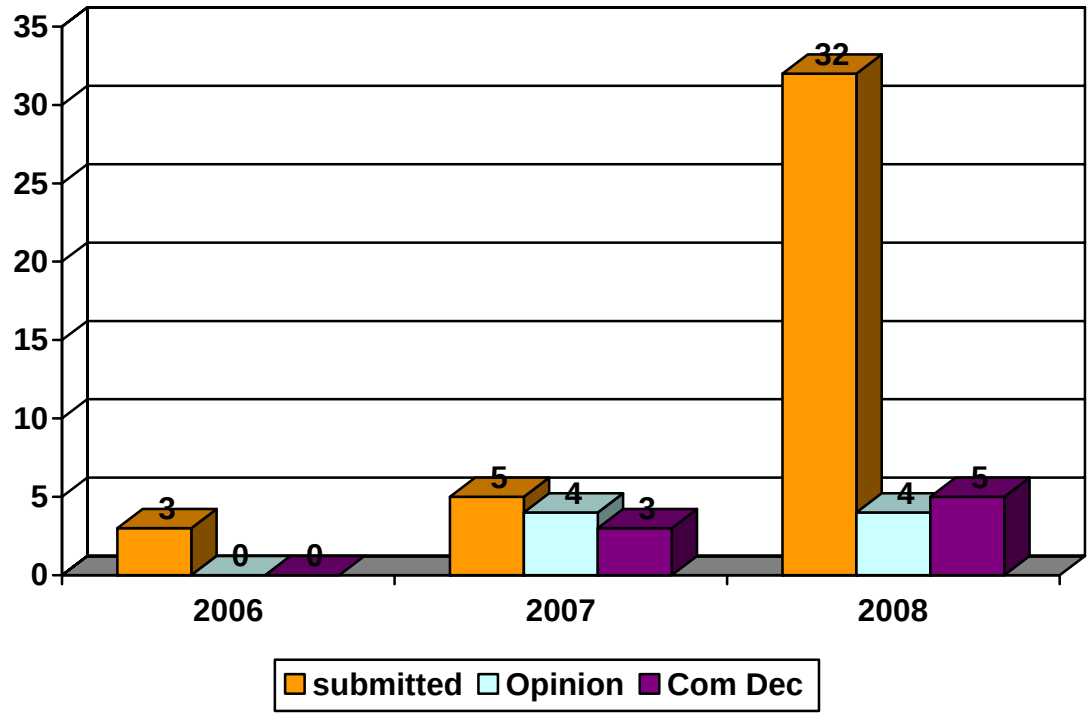
There were 7 biotech products including 2 biosimilar products in 2008. These products make up 10% of all applications with an outcome. There we only 5 products falling under mandatory indications; 3 of those were cancer products, 1 was for treatment of HIV/AID and 1 for diabetes. Some additional characteristics of products falling under the mandatory scope are available in Annex 2.

Optional scope

As noted above there has been a considerable increase in the number of new active substances with an outcome 2008 (n=29). Most (27) of these 29 new active substances were so called "complete stand alone applications" (article 8.3) and 2 were fixed combination (artice10b) applications. It should be noted that the definition of a new

active substance is a legal one and implies that the substance was not authorised in the Community on the date of entry into force of Regulation 726/2004 (20 November 2005).
In 2008, the first over the counter (OTC) product (Orlistat) was approved by the Scientific Committee. There was the same proportion of "significant innovation/patient interest" products in 2008 as in 2007. Also the proportion of generics was about the same 2008 as 2007 although the actual number of generic applications is on a considerable increase as indicated in Figure 2. Some characteristics of products falling under the optional scope are available in Annex 2**.**

Figure 2. Chemical Generics in the Centralized Procedure - Ongoing and those with outcomes.



Legal basis

Sixty-one (87%) of the 70 applications with an outcome in 2008 were complete stand-alone applications, 4 were generics, 2 were biosimilars, and 3 were fixed combinations.

So called informed consent applications were not included here since they were regarded as part of the "multiple application"- category and thus excluded from this analysis. However, overall there we 11 "informed consent" applications of a total of 92 applications with an outcome in 2008.

1.3. Early approval

Conditional approval

Both Intelence and Tyverb were formally approved conditionally by the CHMP in 2008. Tyverb, however, whilst receiving a conditional approval by majority in 2007 (table 2), the opinion was revisited in 2008 due to safety concerns and the positive opinion was confirmed. Intelence was approved by consensus for treatment of HIV infection in 2008.

Approval under exceptional circumstances

There were 3 products approved under exceptional circumstances during 2008 (table 2): Ceplene, an orphan designated product was approved by majority in acute leukaemia after a re-examination procedure. Pandemrix and Celvaplan were approved by consensus for prophylaxis of influenza in an officially declared pandemic situation.

Table 2 Products with conditional approvals and approval under exceptional circumstances

	Outcome Year				
Opinion	2004	2005	2006	2007	2008
Normal	26 (89.7)	20 (87)	33 (84.6)	38 (82.6)	42 (91.3)
Exceptional	3 (10.3) a	3 (13) b	3 (6.7) c	5 (10.8) d	3 (6.5) g
Conditional	NA	NA	3 (7.6) e	3 (6.5) f	1 (2.2) h
Total Positive	29 (100)	23 (100)	39 (100)	46 (100)	46 (100)

a EC* 2004,	Orfadin, Prialt, Velcade
b EC 2005	Aptivus, Naglazyme, Revatio
c EC 2006	Atryn, Elaprase, Evoltra
d EC 2007	Atriance, Daronix, Focetria, Increlex, Yondelis
e CA** 2006	Diacomit, Prezista, Sutent
f CA 2007	Isentress, Vectibix, Tyverb
g EC 2008	Celvapan, Ceplene, Pandemrix
h CA 2008	Intelence

* EC: Exceptional Circumstances ** CA: Conditional Approval

Products with accelerated assessments

Table 3 depicts applications during 2007 and 2008 where the CHMP started the assessment under the accelerated procedure aiming for an opinion after 150 days of assessment. However, only 2 applications (Isentresss and Soliris) in 2007 and none in 2008 fulfilled the 150 days assessment procedure criterion. These applications reverted to normal timetables following questions being raised by the Committee and subsequent needs for longer clock-stops and prolonged assessments by the Committee.

Table 3. Products initially reviewed under the accelerated assessment procedure, 2007 and 2008

2007			
Name of product	**Therapeutic Area**	**Active Time**	**Clock stop**
Maraviroc (Celsentri)	HIV infection	169	35
Inactivated pandemic strain. Whole virion (Daronix)	Pandemic Influenza	142	174
H5N1 virus surface inactivated antigen (Focetria)	Pandemic Influenza	162	224
Raltegravir (Isentress)	HIV infection	141	35
Eculizumab (Soliris)	Paroxysmal nocturnal hemoglobinuria	147	36
Influenza vaccine (cell culture) (Optaflu)	Prophylaxis of influenza for adults (seasonal)	202	79
2008			
Prepandrix	influenza vaccine	189	204
Pandemrix	prophylaxis of influenza	161	204
Firazyr	treatment of hereditary angioedema	204	49
Vidaza II*	antineoplastic	198	69

* II signifies resubmission.

1.4. Article 58 opinions

There were no such applications with an outcome during 2008

1.5 Characteristics of Products with positive and negative outcomes (withdrawals and negative opinions)

Annex 1 A and B displays some characteristics on applications with positive and negative outcomes 2008.

There were 47 (67%) applications with a positive outcome in 2008 and 23 (33%) with a negative outcome (table 4). This negative outcome rate is somewhat higher than the "normal" average which used to be around 25%. It can be noted that SMEs contribute with 30% of the negative outcomes. The negative outcome rate among SMEs thus amounted to 58% (7/12) (see also section 1.6."Marketing Authorisation applications from Small and Medium Sized Companies", below).

There were 19 orphan designated products with an outcome in 2008; 9 with a positive and 10 with a negative outcome thus "contributing with 43% of the negative outcomes. The negative outcome rate among orphan designated products thus amounted to 53% (10/19). (See also section 1.3 "Marketing Authorisation Applications (MAAs) with Orphan status and Scientific Advice/Protocol assistance", below)

It is noted that 10 of the orphan designated products were pursued by SMEs. Six of these 10 were unsuccessful. On the other hand 4 of the remaining 9 orphans (not SMEs) were also unsuccessful.

Table 4 thus suggests that SMEs and orphan medicinal products contribute to a high negative outcome rate. In total the negative outcome rate for applications eligible via the mandatory scope was 42% (13/31) but not counting the applications for orphan medicinal products only 3 (25%) of the remaining 12 applications eligible via the mandatory scope (biotech and mandatory indications) had a negative outcome. In total the negative outcome rate for applications eligible via the optional scope was 26% (10/39). Nine of these 10 were for new active substances.

It is noted that scientific advice was given to similar extents irrespective of outcome.
These 3 aspects (SME, orphans, scientific advice) are currently investigated in a special analysis of factors important for outcomes and will be published.

As can be expected, applications with negative outcomes had distinctively higher proportions of different major objections (MO) than those with positive outcomes raised by the CHMP after the first review cycle, i.e. at the time of the Day 120 List of Questions (table 4).

Some additional characteristics of orphan medicinal products and SME's applications are displayed in Annexes 4 and 5.

Table 4 Characteristics and frequencies of applications with positive and negative outcomes and of Major Objections (MO).

Characteristic	**Pos. outcomes**	**Neg. outcomes**	**Neg. outcome rate**
Total number (no duplicates)	47	23	23/70 (33%)
SME	5 (11%)	7 (30%)	7/12 (58%)
Non SME	42 (89%)	16 (70%)	16/58 (28%)
Orphans	9 (19%)	10 (43%)	10/19 (53%)
Non Orphans	39 (83%)	13 (57%)	13/52 (25%)
SA	26 (55%)	13 (56%)	13/39 (33%)
MO on "design"	4 (9%)	9 (39%)	9/13 (69%)
MO on "patient population"	12 (26%)	8 (35%)	8/20 (40%)
MO "endpoint"	9 (19%)	8 (35%)	8/17 (47%)
MO on "magnitude of effect"	7 (15%)	11 (48%)	11/18 (61%)
MO on "Validity of clinical trial"	4 (9%)	3 (13%)	4/7 (57%)

1.6 Marketing Authorisation Applications (MAAs) with Orphan status and Scientific Advice/Protocol assistance

MAAs with Orphan status

Table 5 shows orphan designated drugs approved since 2005 as proportions of all approved that year. There were 9 products approved in 2008 and these made up 19% of all approved applications this year. One product (Ceplene) of these 9 products was approved under exceptional circumstances. As discussed, there were also 10 orphan designated products that received a negative outcome from the Scientific Committee (table 6). As mentioned, marketing authorisation applications for orphan designated medicinal products constitute a significant proportion of applications with negative outcomes and further analyses of factors important for outcome is underway. Annex 3 shows some additional information on orphan medicinal products with an outcome in 2008.

Table 5: Proportion of positive outcomes for orphans of all MAAs with a positive outcome.

	2005	**2006**	**2007**	**2008**
Orphan Drugs	3/23 (13%)	11/45 (24%)	9/51 (18%)	9/47 (19%)

Table 6: Proportion of negative outcomes for orphans of all MAAs with a negative outcome.

	2005	**2006**	**2007**	**2008**
Orphan Drugs	5/13 (38%)	4/11 (36%)	8/17 (47%)	10/23 (43%)

MAAs with Scientific Advice (includes protocol assistance)

This year 2008, 39 (56%) of 70 applications with an outcome were preceded by SA (figure 3). Thus, an increasing proportion of MAAs is preceded by SA. In 2007, 47% of applications were preceded by scientific advice.

As indicated above, around 55% of applications (irrespective of outcome) received SA prior to marketing authorisation application. As mentioned, this latter aspect is subject to an ongoing analysis which will be published.

A continued rise in the number of requests for SA / PA is expected in 2009 and 2010. Moreover, a significant increase in the number of requests for SA on topics such as innovative statistical approaches and adaptive clinical study designs is expected. The majority of requests to date (> 50%) have covered clinical development, followed by pre-clinical (~ 30%) and quality aspects (~ 15%). This trend is also likely to continue into 2009 and 2010.

Included in these figures are 16 (84%) of the 19 orphan designated products that had protocol assistance before the marketing authorisation application.

Figure 3: Proportion of MAAs that received SA (by outcome year)

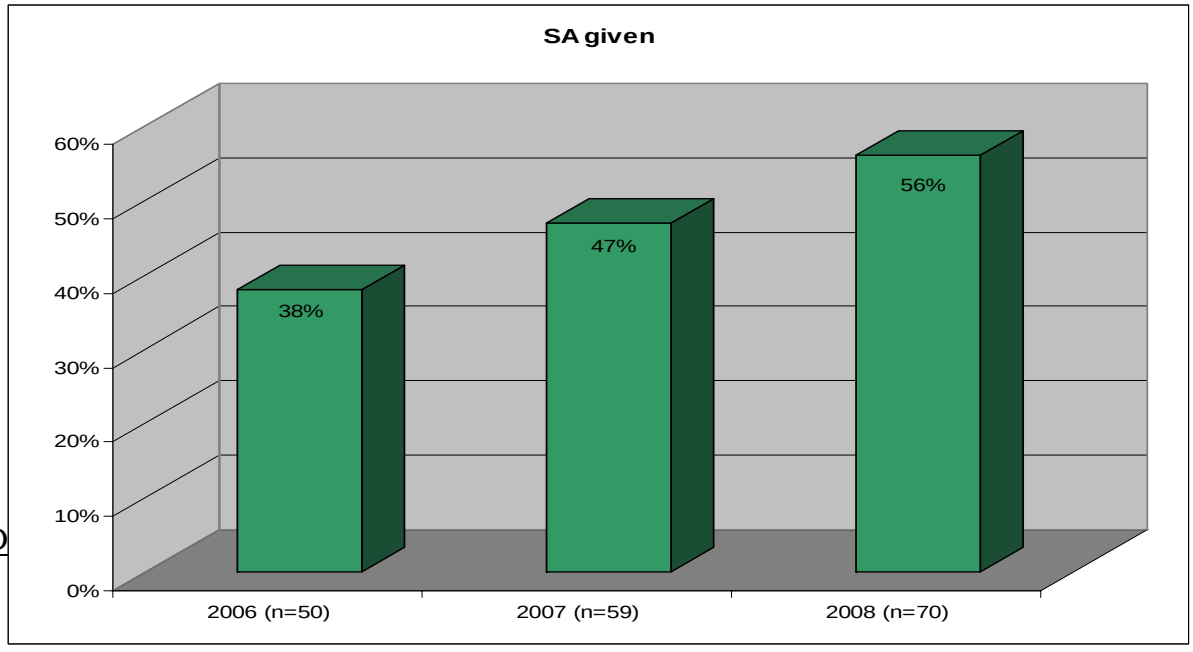


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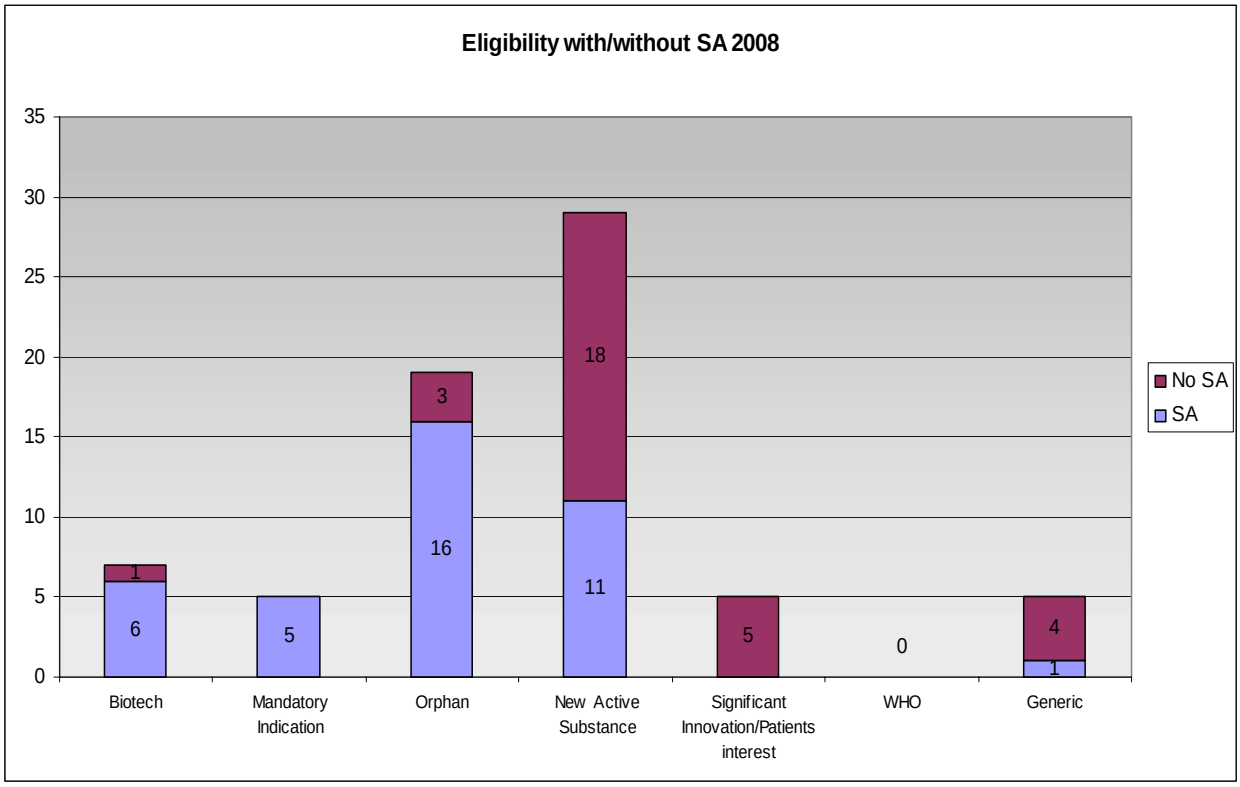
Figure 4 shows the numbers and distribution of SA over eligibility to the centralized procedure. The figure indicates that the highest proportion of scientific advice was given to products belonging to the mandatory scope.

Figure 4. Distribution of Scientific Advice over eligibility



1.7 Marketing Authorisation applications from Small and Medium Sized Companies (SMEs)

There were 12 (17%) applications from SMEs in 2008 (table 4). The experience with these applications is still limited and has been summarized in an overall assessment recently published on the EMEA web site by the SME office:

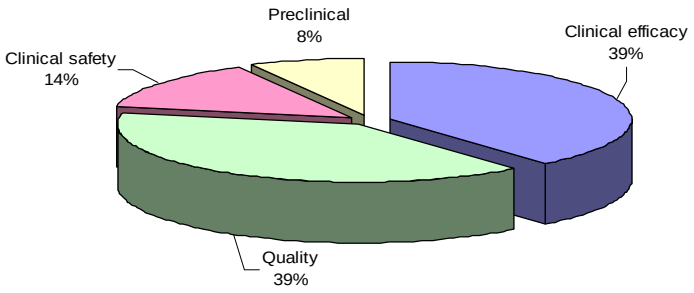
Since December 2005, thirty-eight SME companies have submitted MAAs, 33 for human medicinal products. Of the human medicinal products that have been subject of MAAs, 6 have received positive outcomes and 12 have resulted in negative outcomes (3 negative opinions and 9 withdrawals). Fifteen applications are currently ongoing. A preliminary analysis into the impact of scientific advice at the stage of the marketing application has shown that many small companies in particular do not take the advice fully into account. The following observations can be made on the 18 applications from SMEs for medicinal products for human use that have received an outcome to date:

- Overall 55 % (10/18) had previously sought scientific advice. Of those companies with a positive outcome 83% (5/6) had received EMEA advice. Of those with a negative outcome, 42% (5/12) had previously sought advice but only one company (8%) had taken the advice into account and as such qualified for a conditional fee exemption.

- Seventy-two percent (13/18) of the applications were for designated orphan medicinal products, 83% of those with a positive outcome and 66% of those with a negative outcome.
- One application, for the orphan medicinal product Soliris, was reviewed to an accelerated timetable and received a positive opinion from the CHMP in 147 days.
- The average active time for the 18 applications from SMEs was 181 days.
- The majority of companies requested additional time to respond to questions raised by the CHMP during the procedure.
- The average response (so-called "clock-stop") time for SME companies was 7 months.
- On average 9 major objections per application were raised by CHMP at day 120 of the procedure.
- A breakdown of the areas where major objections arose is provided in figure 5**.**
- The agency has noted that major objections ran particularly high in the area of quality. The SME workshop in 2008, which focussed on quality, aimed to increase awareness of this important aspect of development. A number of applicants have indicated their intention to seek scientific advice and re-submit applications once further data has been generated suggesting that some of the applications were filed prematurely.

Annex 4 displays some additional characteristics for SME products.

Figure 5 Major objections in Day 120 List of Questions for SMEs (18 MAAs**)**



1.8 Medicinal products of notable public health interest

Some characteristics of such products are outlined in Annex 5.

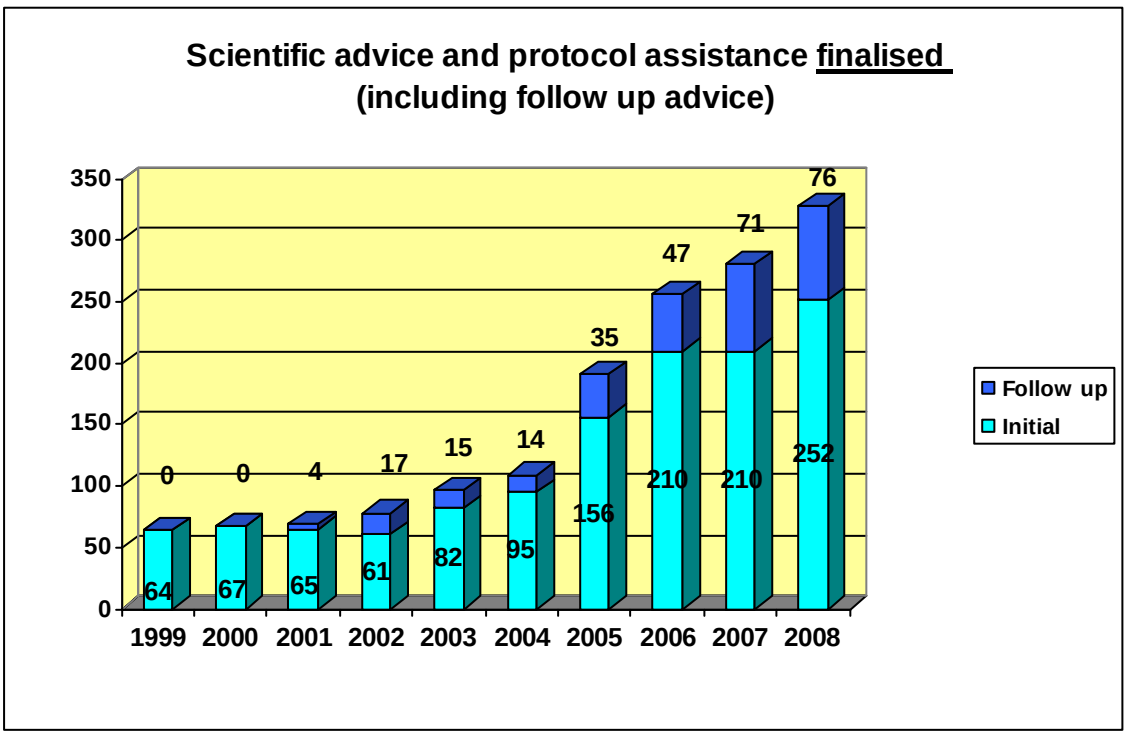
2. Applications for CHMP Scientific Advice/Protocol Assistance

The marked increase in the numbers of SA/PA was sustained in 2008. A further increase from 281 to 328 procedures was even observed (Fig. 6). During 2008 SA/PA was provided according to the new procedure which had been published on the EMEA website on 26 April 2006 and implemented as of July 2006.

- The procedure of 40 or 70 days could be followed with only 4 exceptions out of 328 procedures
- The CHMP received 3requests for broader and more general advice for specific types of medicinal products or treatments as compared to 2 requests in 2007.

- The number of SA requests on acceptability of the development programme for conditional marketing authorisation remained steady (20 requests in 2007, 21 requests in 2008) and the development programme for marketing authorisation application under exceptional circumstances (6 requests in 2007, 4 in 2008) were also being handled.
- Follow-up advices slightly increased from 71 in 2007 to 76 in 2008.
- The number of protocol assistance given decreased (65 handled in 2008 compared to 72 in 2007, a drop of 6% compared to 2007)
- During 2008 one work-shop was held together with EFPIA on "Pharmacokinetics and Pharmacogenetics in drug development".
- Biomarkers pay an increasingly important role in drug development and Industry has expressed strong wish to receive SA from the EMEA on the qualification of biomarkers for certain use in drug development. A guidance document for Companies seeking to qualify new innovative procedures (including biomarkers) was drafted, published for consultation in June 2008 and after implementation of comments adopted by the CHMP as final in January 2009. In addition the first CHMP pilot biomarker qualification opinion was published in June 2008 and finalised in January 2009. Three more qualification procedures were initiated in 2008.
- A new peer review system of the final advice letters was also introduced in 2008. For each procedure a SAWP peer reviewer will be appointed to ensure consistency with the discussion held at the SAWP meeting and the final advice letter and general readability. For special important issues CHMP peer review groups were formed by therapeutic area, who peer-review the final advice letter before it is adopted at the CHMP plenary session.
- Fifty-nine (59) SME companies requested scientific advice from the agency in 2008, compared to fifty (50) the previous year.

Figure 6



3. Applications for Orphan status

In 2008 one hundred and nineteen applications were submitted and eighty six positive opinions were adopted. For the fifth consecutive year, more than hundred applications were received for designation as orphan medicinal product. The ratio designation / application is 0.72, similar to past years and higher than 0.7 since 2005.

The number of withdrawn applications (31) was higher than in the previous 4 years. The Committee for Orphan Medicinal Products (COMP) adopted only 1 negative opinion.
After the implementation of the common EMEA/FDA application form for orphan designation a total of 40 applications using this form have been received (38% of the total applications submitted).

The average time taken by the COMP to evaluate applications was 66 days, which means that many opinions were adopted after a first discussion at the COMP without the need for list of questions or oral explanation. The EMEA managed to publish all public summaries of opinions after designation within one month after adoption of the Commission decision.

With regards to the therapeutic areas attracting most designations, oncology has been the most represented with more than 35% of positive opinions on designation, followed by products for the musculoskeletal and nervous system (20%) and cardiovascular and respiratory systems (9%). The number of innovative products designated has been very high, with 47 of the 86 positive opinions (55%) being biotechnology products. Amongst them, the Committee has designated fusion proteins, several monoclonal antibodies, cell therapy products and an oligonucleotide.
For 2008 a special contribution of € 6 million was granted by the Community. The Agency processed requests for fee reductions for designated orphan medicinal products totalling € 4 767 500, financed by the special contribution. In 2009 the fee reduction policy has been revised aiming at increased support for SME s. In the revised policy for 2009, the fee reduction for new applications for marketing authorisation to SMEs is increased to 100%. The fee reduction for post authorisation activities including annual fees to SMEs in the first year after granting a marketing authorisation is also increased to 100%.
Up to date more than 50 orphan medicines had been granted a marketing authorisation (MA) by the European Commission (some for more than one orphan indication). These MAs cover more than 45 different orphan indications, including those extensions of indications that have been accepted from the initial MA. The median prevalence of the conditions for which designated medicinal products are available is 0.7 in 10,000 (range, 0.001 to 4.9 in 10,000). Twenty-four marketed indications are conditions with prevalence of less than one in 10,000, and seventeen designated products are marketed for conditions with prevalence ranging from one to three in 10,000 people. More than 70% of the products authorised had to demonstrate significant benefit, and in the remaining cases the product was the first to receive an MA in the orphan condition.

4. Applications for SME status

Since the EMEA introduced provisions for SMEs in December 2005, 372 companies have had SME status actively assigned by the EMEA. The large majority of companies are developing medicinal products for human use, 14 are veterinary companies, 15 companies are developing products for both human and veterinary use and 35 are regulatory consultants.

In 2008, the number of companies requesting SME status from the agency increased by 50% compared to the previous year. The number of renewal requests increased by 91% compared to 2007.

Looking at the types of product under development, the broad breakdown into chemical entities vs. biologics is 40% and 60% respectively. Although the large majority (70%) of companies are yet to place a product on the market, just over half (54%) have reached the clinical phase of development – with some 20% in late phase clinical trials.

ANNEX 1

Some characteristics of the applications that reached positive and negative outcomes during 2008

Table A: Applications (n= 47) with positive outcomes during 2008.
Table B: Applications (n= 23) with negative outcomes during 2008

1A – positive outcomes

Product Name	INN Common Name	Active Time	Clock Stop	Scientific Advice	Paedic Indic	Therapeutic Area
Tyverb	Lapatinib	202	212	Given	NO	Breast cancer
Effentora	Fentanyl citrate	204	105	Not-Given	NO	Pain in cancer
Pradaxa	Dabigatran etexilate	205	132	Not-Given	NO	Venous thrombosis
Thalidomide Pharmion	Thalidomide	177	160	Given	NO	Myeloma
Adenuric	Febuxostat	188	324	Not-Given	NO	Hyperuricaemia
Mycamine II	Micafungin	203	435	Given	NO	Fungal infections
Pandemrix	H5N1 split antigen influenza vaccine, adjuvanted with AS03	161	204	Not-Given	NO	Influenza
Prepandrix	Purified antigen fractions of inactivated split virions a/ ietnam/1194/2004 nibrg-14 (h5n1	189	204	Not-Given	NO	Influenza
Privigen	Human normal immunoglobulin	188	177	Not-Given	YES	Immune-mediated diseases
Filgrastim ratiopharm	Filgrastim	209	156	Given	YES	Neutropenia
Volibris	Ambrisentan	205	132	Given	NO	Pulmonary arterial hypertension
Ceplene II	Histamine	202	309	Not-Given	NO	Acute myeloid leukaemia
Trepedative	Nicotinic acid / laropiprant	202	77	Given	NO	Hypercholesterolaemia or Dyslipidaemia
Firazyr	Icatibant	204	49	Given	NO	Hereditary angioedema
Janumet	Sitagliptin/metformin hydrochloride	207	133	Given	NO	Type 2 Diabetes Mellitus
Latixa	Ranolazine	177	307	Not-Given	NO	Angina pectoris

Relistor	Methylnaltrexone bromide	204	133	Given	NO	Constipation
Bridion	Sugammadex	203	112	Given	NO	Neuromuscular block
Doribax	Doripenem monohydrate	202	113	Not-Given	NO	Bacterial infections
Intelence	Etravirine	178	138	Given	NO	HIV-1 infection
Opgenra	Recombinant human osteogenic protein-1/eptotermin	202	289	Given	NO	Spondylolisthesis
Vimpat	Lacosamide	209	191	Not-Given	YES	Epilepsy
Oprymea	Pramipexole	177	41	Not-Given	NO	Parkinson's disease
Evicel	Human fibrinogen / human thrombin	207	137	Not-Given	NO	Haemostasis .
Olanzapine Mylan	Olanzapine	177	34	Not-Given	NO	Schizophrenia
Xarelto	Rivaroxaban	181	63	Given	NO	Venous thromboembolism
Kuvan	Sapropterin hydrochloride	200	107	Given	YES	Phenylketonuria
Zypadhera	Olanzapine pamoate	198	235	Given	NO	Schizophrenia
Azarga	Brinzolamide / timolol	177	97	Not-Given	NO	Glaucoma or ocular hypertension
Zevtera	Ceftobiprole medocaril	175	314	Given	NO	Complicated skin and soft tissue infections
Nplate	Romiplostim	203	162	Given	NO	Thombocytopenic purpura
Irbesartan krka	Irbesartan hydrochloride	177	34	Not-Given	NO	Hypertension
Rasilez HCT	Aliskiren hemifumarate / hydrochlorothiazide	195	135	Not-Given	NO	Hypertension
Lunivia	Eszopiclone	205	230	Not-Given	NO	Insomnia
Stelara	Ustekinumab	204	123	Given	NO	Plaque psoriasis
Filgrastim Hexal	Filgrastim	204	216	Given	YES	Neutropenia
Pramipexole Teva	Pramipexole	196	141	Not-Given	NO	Parkinson's disease
Vidaza II	Azacitidine	198	69	Not-Given	NO	Myelodysplastic syndrome, Leukemia
RoActemra	Tocilizumab	205	125	Given	NO	Rheumatoid arthritis

Valdoxan II	Agomelatine	203	217	Given	NO	Depression
Celvapan	Pandemic influenza vaccine (h5n1, whole virion, vero cell derived, inactivated)	205	90	Given	NO	Influenza in an officially declared pandemic situation.
Efient	Prasugrel	204	91	Given	NO	Acute Coronary Syndrome
Fablyn	Lasofoxifene	203	120	Not-Given	NO	Osteoporosis
Firmagon	Degarelix	195	72	Given	NO	Prostate cancer
Intanza	Split viron inactivated	205	153	Not-Given	NO	Influenza
Ixiaro	Japanese encephalitis virus	204	119	Given	NO	Japanese B encephalitis
Mepact	Mifamurtide	205	552	Given	YES	Osteosarcoma

1 B – Negative outcomes

Product Name	INN	Active Time	Clock Stop	Scientific Advice	Paedic Indic	Therapeutic Area
Mylotarg	Gemtuzumab ozogamicin	200	431	Given	YES	Acute Myeloid Leukaemia
Cimzia	Certolizumab pegol	202	338	Not-Given	NO	Crohn's Disease
Kiacta	Eprodisate disodium	202	240	Given	NO	Amyloidosis
Rhucin	Rhc1inh	176	308	Given	NO	Hereditary angioedema
Lenalidomide Celgene Europe	Lenalidomide	176	672	Given	NO	Myelodysplastic syndromes
Pristiqs	Desvenlafaxine succinate monohydrate	193	309	Given	NO	Vasomotor symptoms
Ramelteon	Ramelteon	211	225	Not-Given	NO	Insomnia
DuoCover	Clopidogrel hydrogen sulphate/acetylsalicylic acid	205	132	Not-Given	NO	Acute coronary syndrome
OrBec	Beclomethasone dipropionate	205	342	Not-Given	NO	Gastrointestinal Graft vs. Host disease
Aquilda	Satavaptan	117	221	Not-Given	NO	Hyponatremia
Aflunov	Pre-pandemic avian influenza vaccine, H5N1, surface antigen, inactivated, adjuvated with MF59.1	190	379	Given	NO	Influenza
Spanidin II	Gusperimus trihydrochloride	194	344	Given	NO	Wegeners granulomatosis
Diractin	Ketoprofen	176	252	Not-Given	NO	Osteoarthritis
Sovrima	Idebenone	203	141	Given	YES	Friedreich's Ataxia
Orplatna	Satraplatin	172	206	Given	NO	Prostate cancer
Ixempra	Ixapebilone	203	189	Not-Given	NO	Prostate cancer
Exulett	Dalbavancin	174	217	Not-Given	NO	Bacterial infection

Ellefore	Desvenlafaxine	166	188	Given	NO	Depression
Lacosamide Pain UCB Pharma	Lacosamide	176	231	Not-Given	NO	Neuropathic pain
Vibativ	Telavancin	201	316	Not-Given	NO	Complicated skin and soft tissue infections
Vekacia	Ciclosporine	175	282	Given	NO	Keratoconjunc-tivitis
Theraloc	Nimotuzumab	173	230	Given	YES	Glioma
Advexin	Contusugene ladenovec	174	183	Given	NO	Li-Fraumeni cancer

ANNEX 2

Some characteristics of 70 products with an outcome during 2008 based on eligibility categories

MANDATORY SCOPE

Biotech

Product Name	INN	Therapeutic Area	ATC Code
Cimzia	Certolizumab pegol	Crohn's Disease	L04AB05
Filgrastim ratiopharm	Filgrastim	Neutropenia	L03AA02
Opgenra	Recombinant human osteogenic protein-1/eptotermin	Spondylolisthesis	MO5BC02
Aflunov	Pre-pandemic avian influenza vaccine	H5N1 avian influenza	J07BB02
Stelara	Ustekinumab	Plaque psoriasis	L04AC
Filgrastim Hexal	Filgrastim	Neutropenia	L03AA02
RoActemra	Tocilizumab	Rheumatoid arthritis	L04AC07

Mandatory Indication

Product Name	INN	Therapeutic Area	ATC Code_
Tyverb	Lapatinib	Breast cancer	L01XE07
Janumet	Sitagliptin/metformin hydrochloride	Diabetes Mellitus	A10BD07
Intelence	Etravirine	HIV-1 infection	J05AG04
Orplatna	Satraplatin	Prostate cancer	L01XA04
Firmagon	Degarelix	Prostate cancer	L02BX02

Orphan designated products

Product Name	INN	Therapeutic Area	ATC Code_
Lenalidomide Celgene Europe	Lenalidomide	Myelodysplastic syndromes	L04AX04
Mylotarg	Gemtuzumab ozogamicin	Acute Myeloid Leukaemia	L01XC05
Rhucin	RhC1INH	Hereditary angioedema	C01
Kiacta	Ceprodisate disodium	Amyloidosis	V03AX
Ceplene II	histamine	Acute myeloid leukaemia (AML)	L03AX14
Mepact	Mifamurtide	Non-metastatic osteosarcoma	L03AX15
OrBec	Beclomethasone dipropionate	Gastrointestinal Graft vs. Host disease	A07EA07
Spanidin II	Gusperimus trihydrochloride	Wegeners granulomatosis	L04AA19
Thalidomide Pharmion	Thalidomide	Myeloma	LO4AX02
Volibris	Ambrisentan	Pulmonary arterial hypertension	CO2KX02
Firazyr	Icatibant	Hereditary angioedema	C01EB19
Vekacia	Ciclosporine	Ophthalmology	L04AA01
Sovrima	Idebenone	Friedreich's Ataxia	N
Advexin	Contusugene ladenovec	Li-Fraumeni cancer	L01
Theraloc	Nimotuzumab	Glioma	L01XC
Nplate	Romiplostim	Immune thrombocytopenic purpura	B02BX04
Kuvan	Sapropterin hydrochloride	Phenylketonuria	A16A X07
Ixiaro	Japanese encephalitis virus (nactivated, adsorbed)	Japanese B encephalitis	J07BA02
Vidaza II	Azacitidine	Myelodysplastic syndrome, leukemia	L01BC07

II indicates resubmission

OPTIONAL

New Substance

Product Name	INN	TherapeuticArea	ATC Code
Pradaxa	Dabigatran etexilate	Venous thromboembolism	B01AE07
Adenuric	Febuxostat	Chronic hyperuricaemia	M04AA03
Mycamine II	Micafungin	Fungal infections	J02AX05
Pandemrix	H5N1 split antigen influenza vaccine, adjuvanted with AS03	Influenza	J07BB02
Prepandrix	Purified antigen fractions of inactivated split virions a/ ietnam/1194/2004 nibrg-14 (h5n1	Influenza	J07BB02
Pristiqs	Desvenlafaxine succinate monohydrate	Vasomotor symptoms	N06AX23
Trepedative	Nicotinic acid / laropiprant	Hypercholesterolaemia or dyslipidaemia	C10AD52
Latixa	Ranolazine	Angina pectoris	C01EB18
Relistor	Methylnaltrexone bromide	Opioid-induced constipation	A06
Bridion	Sugammadex	Neuromuscular block	V03AB35
Doribax	Doripenem monohydrate	Bacterial infections	J01DH04
Ramelteon	Ramelteon	Insomnia	N05CH02
DuoCover	Clopidogrel hydrogen Sulphate/acetylsalicylic acid	Acute coronary syndrome	B01
Aquilda	Satavaptan	Hyponatremia	C03
Vimpat	Lacosamide	Epilepsy	N03AX18
Xarelto	Rivaroxaban	Venous thromboembolism	B01AX06
Azarga	Brinzolamide / timolol	Glaucoma or ocular hypertension	S01ED51
Zevtera	Ceftobiprole medocaril	Skin and soft tissue infections	J01DI01
Ixempra	ixapebilone	Breast cancer	L01DC04
Rasilez HCT	Aliskiren hemifumarate /	Hypertension	C09XA52

	hydrochlorothiazide		
Lunivia	Eszopiclone	Insomnia	N05CF04
Valdoxan II	Agomelatine	Depression	N06AX22
Exulett	Dalbavancin	Bacterial infections	J01XA
Ellefore	Desvenlafaxine	Depression	N06A
Lacosamide Pain UCB Pharma	Lacosamide	Neuropathic pain	N03A
Vibativ	Telavancin	Skin and soft tissue infections	J01
Celvapan	Pandemic influenza vaccine (h5n1, whole virion, vero cell derived, inactivated)	Prophylaxis of H5N1Pandemic influenza in an officially declared pandemic situation.	J07BB01
Efient	Prasugrel	Acute coronary syndrome	B01
Fablyn	Lasofoxifene	Osteoporosis	M05

II indicates resubmission

Significant Innovation

Product Name	**INN**	**Therapeutic Area**	**ATC Code**
Effentora	Fentanyl citrate	Pain in cancer	N02AB03
Privigen	Human Normal Immunoglobulin	Immune-mediated diseases	J06BA02
Diractin	Ketoprofen	Osteoarthritis	M01AE03
Evicel	Human fibrinogen / human thrombin	Haemostasis	B02BC
Intanza	Split viron inactivated	Iinfluenza	J07BB02

Generics

Product Name	INN	Therapeutic Area	ATC Code
Oprymea	Pramipexole	Parkinson's disease	N04B-C
Olanzapine Mylan	Olanzapine	Schizophrenia	N05A H03
Zypadhera	Olanzapine pamoate	Schizophrenia	N05AH03
Irbesartan krka	Irbesartan hydrochloride	Hypertension	C09CA04
Pramipexole Teva	Pramipexole	Parkinson's disease	N04BC

ANNEX 3

Some characteristics of 19 orphan medicinal products with an outcome during 2008.

Product Name	INN	Therapeutic Area	Scientific Advice	Pediatric Indication	SME	Outcome
Lenalidomide Celgene Europe	Lenalidomide	Myelodysplastic syndromes	Given	NO	NO	Negative after appeal by consensus
Mylotarg	Gemtuzumab ozogamicin	Acute Myeloid Leukaemia	Given	YES	NO	Negative after appeal by majority
hucin	Rhc1inh	Hereditary angioedema	Given	NO	YES	Negative after appeal by majority
Kiacta	Eprodisate disodium	Amyloidosis	Given	NO	YES	Withdrawn after appeal
Ceplene II	Histamine	Acute myeloid leukaemia (AML)	Not-Given	NO	YES	Positive after appeal by majority
Mepact	Mifamurtide	Non-metastatic osteosarcoma	Given	YES	YES	Positive by consensus
OrBec	Beclomethasone dipropionate	Gastrointestinal Graft vs. Host disease	Not-Given	NO	YES	Withdrawn prior to opinion
Spanidin II	Gusperimus trihydrochloride	Wegeners granulomatosis	Given	NO	NO	Withdrawn prior to opinion
Thalidomide Pharmion	Thalidomide	Myeloma	Given	NO	NO	Positive by consensus
Volibris	Ambrisentan	Pulmonary arterial hypertension	Given	NO	NO	Positive by consensus
Firazyr	Icatibant	Hereditary angioedema	Given	NO	YES	Positive by consensus
Vekacia	Ciclosporine	Ophthalmology	Given	NO	YES	Withdrawn prior to opinion
Sovrima	Idebenone	Friedreich's Ataxia	Given	YES	YES	Negative after appeal by consensus
Advexin	Contusugene ladenovec	Li-Fraumeni cancer	Given	NO	NO	Withdrawn prior to opinion

Theraloc	Nimotuzumab	Glioma	Given	YES	YES	Withdrawn prior to opinion
Nplate	Romiplostim	Immune thombocytopenic purpura	Given	NO	NO	Positive by consensus
Kuvan	Sapropterin hydrochloride	Phenylketonuria	Given	YES	NO	Positive by consensus
Ixiaro	Japanese encephalitis virus	Japanese B encephalitis	Given	NO	YES	Positive by consensus
Vidaza II	Azacitidine	Myelodysplastic syndrome, leukemia	Not-Given	NO	NO	Positive by consensus

II: indicates resubmission

ANNEX 4

Some characteristics of the 12 products from SMEs and an outcome 2008.

Product Name	INN	Therapeutic Area	Orphan	Paediatric Indication	Outcome	Scientific Advice
Kiacta	Eprodisate disodium	Amyloidosis	YES	NO	Withdrawn after appeal	Given
Rhucin	rhC1INH	Hereditary angioedema	YES	NO	Negative after appeal by majority	Given
Ceplene II	Histamine	Acute myeloid leukaemia	YES	NO	Positive after appeal by majority	Not-Given
Firazyr	Icatibant	Hereditary angioedema	YES	NO	Positive by consensus	Given
OrBec	beclomethasone dipropionate	Gastrointestinal Graft vs. Host disease	YES	NO	Withdrawn prior to opinion	Not-Given
Sovrima	Idebenone	Friedreich's Ataxia	YES	YES	Negative after appeal by consensus	Given
Mepact	mifamurtide	Osteosarcoma	YES	YES	Positive by consensus	Given
Theraloc	nimotuzumab	Glioma	YES	YES	Withdrawn prior to opinion	Given
Diractin	Ketoprofen	Osteoarthritis	NO	NO	Withdrawn prior to opinion	Not-Given
Evicel	Human fibrinogen / human thrombin	Haemostasis	NO	NO	Positive by consensus	Not-Given
Vekacia	ciclosporine	Keratoconjunctivitis	YES	NO	Withdrawn prior to opinion	Given
Ixiaro	Japanese encephalitis virus	Japanese B encephalitis	YES	NO	Positive by consensus	Given

II indicates resubmission.

ANNEX 5

Public-health benefits of medicines recommended for approval in 2008

Medicinal products of **notable** public-health interest (e.g. novel technologies, first-in-class, breakthrough products, etc)

- The first medicinal product for use as maintenance treatment in adults with acute myeloid leukaemia, a type of cancer affecting the white blood cells, in combination with interleukin-2 (an anticancer medicine). It is used during the patients' first 'remission' (a period without symptoms of the disease after the first course of treatment). [Ceplene (histamine dihydrochloride)]

- A designated orphan medicinal product to treat high-grade non-metastatic osteosarcoma (a bone cancer) in children, adolescents and young adults. It is used with other anticancer medicines after the cancer has been removed by surgery. [Mepact (mifamurtide)]

- A designated orphan medicinal product used in adults with long-term immune thrombocytopenic purpura (ITP), a disease in which the patient's immune system destroys the platelets (components in the blood that help it to clot). Patients with ITP have low platelet counts and are at risk of bleeding. [Nplate (romiplostim)]

- A designated orphan medicinal product used for the treatment of adults who cannot have a bone marrow transplant and suffer from diseases called myelodysplastic syndromes, a group of conditions where too few blood cells are produced by the bone marrow. [Vidaza (azacitidine)]

- A designated orphan medicinal product used to treat hyperphenylalaninaemia (HPA, high levels of phenylalanine in the blood) in patients with the genetic disorders phenylketonuria (PKU) or tetrahydrobiopterin (BH4) deficiency. [Kuvan (sapropterin dihydrochloride)]

- A new compound in an existing class of antiretroviral medicines used to treat adults who are infected with human immunodeficiency virus type 1 (HIV-1), a virus that causes acquired immune deficiency syndrome (AIDS). It shows activity against virus that is resistant to other compounds in this class and offers new treatment options for HIV-infected patients who have already been treated and failed other medicines. [Intelence (etravirine)]

- A medicinal product belonging to a new class of anti-rheumatic biological agents (interleukin-6 receptor antagonist), which can be used in combination with methotrexate, to treat adults with moderate to severe active rheumatoid arthritis (an immune system disease causing inflammation of the joints). It is used in patients who have not responded adequately to or who could not tolerate other treatments, including conventional medicines for rheumatoid arthritis (such as methotrexate) or tumour necrosis factor (TNF) blockers. [Ro-Actemra (tociluzimab)]

- The first vaccine used to vaccinate adults against Japanese encephalitis, a disease that causes inflammation of the brain. Japanese encephalitis can be fatal or lead to long-term disability. It is transmitted by mosquitoes and is most common in South-East Asia and the Far East. [Ixiaro (Japanese encephalitis vaccine, inactivated, adsorbed)]

- Two new mock-up pandemic influenza vaccines intended for the prevention of influenza during an officially declared pandemic situation (a mock-up pandemic vaccine is not intended for stockpiling, but can be used to speed up the availability of a final vaccine in the event of a pandemic, once the pandemic strain has been identified.). [Pandemrix and Celvapan (pandemic influenza vaccines)]

- The first pre-pandemic vaccine used to vaccinate adults against H5N1 subtype of Influenza A virus that may cause avian influenza in humans. It is intended for use

from WHO influenza pandemic phase 3 (pandemic alert with no or very limited human-to-human transmission) onwards. [Prepandrix]

- Two medicinal products used to prevent the formation of blood clots in the veins (venous thromboembolism, VTE) that can be administered by mouth and do not require laboratory monitoring, representing an alternative to conventional therapy by injection. The first product is a factor Xa inhibitor (it blocks factor Xa, an enzyme that is involved in the production of thrombin, which is central to the process of blood clotting) and is used in adults who are undergoing surgery to replace a hip or knee. The second product is used in adults who have had an operation to replace a hip or knee. It is an anticoagulant (prevents the blood from clotting) that blocks thrombin reducing the risk of blood clots forming in the veins. [Xarelto (Rivaroxaban); Pradaxa (dabigatran etexilate)]

II POST-AUTHORISATION ACTIVITIES

This section consists of a detailed analysis of extensions of indications applications reaching a CHMP opinion, or withdrawn prior to it, in 2008.
Although the Scientific Memory Database was not yet operational in 2008 for Post-Authorisation procedures, dedicated tracking systems were used for the various analyses below.

For information on other Post-Authorisation procedures conducted in 2008 (Other Type II variations, Type I variations, Renewals, Annual-reassessments, follow-up measures/specific obligations, and PSURs), please refer to the EMEA Annual Report 2008.

In 2008, the CHMP completed the assessment of 46 applications for extensions of indications for centrally authorised products (CAPs). As 10 of them were duplicate applications, only the remaining 36 applications were taken into account in the various analyses performed and presented below.

1. Review times

The overall, active and clock-stop times 2008 are presented in figure 7 and summarised in table 7, together with review times from 2007. These correspond to the time required to reach the first CHMP opinion. Re-examination procedures and withdrawals prior to CHMP opinion are excluded from this analysis.

In 2008, the review times stabilised; resulting in a slight decrease of the median overall processing time compared to 2007 (216 days vs. 223 days). The review time varies from 60 to 433 days, depending on the number and complexity of requests for supplementary information (RSI).

Figure 7. Kaplan Meier estimate of the overall (overall time equals active review time plus clock-stop time), active and clock-stop times for 2007 and 2008.

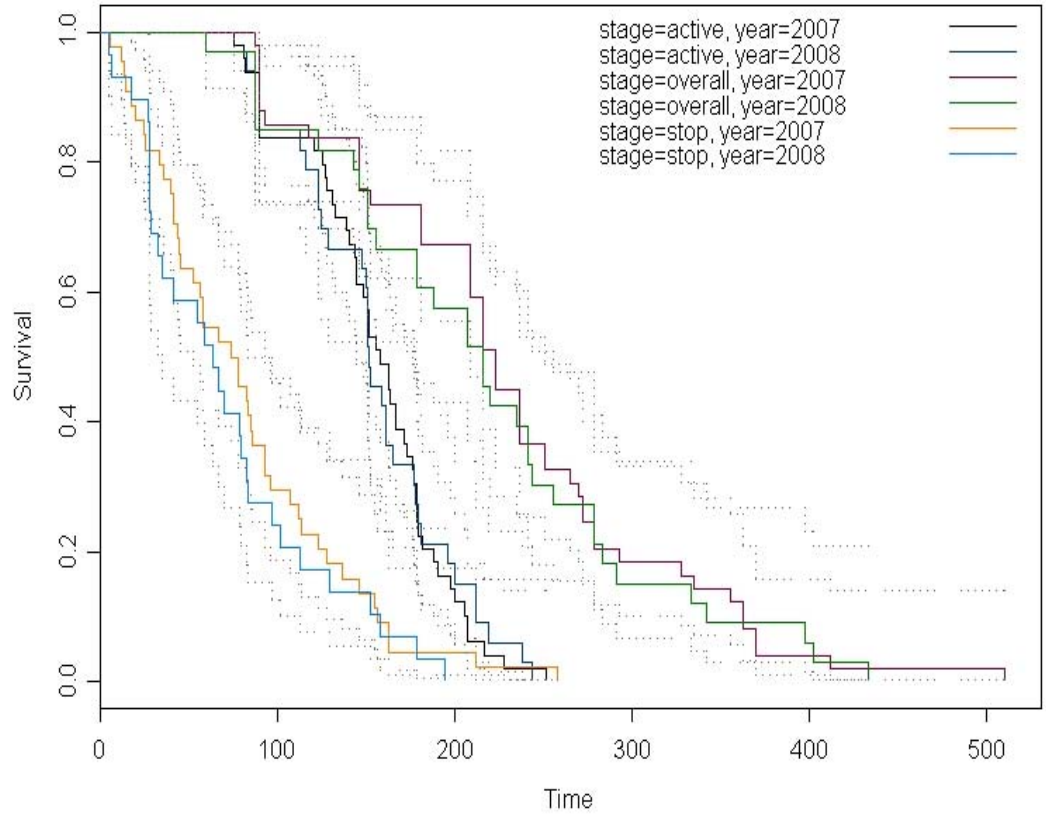


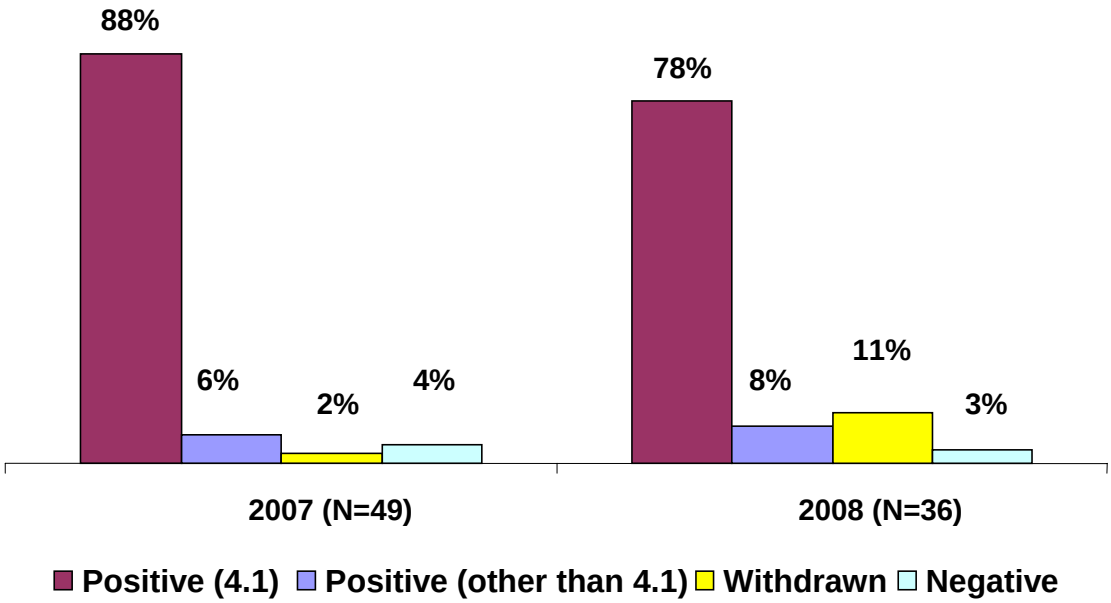
Table 7. Overview of overall, active and clock-stop times for 2007 and 2008

	2007	**2008**
Overall processing time		
Median (95% CI)	223 (209,251)	216 (179,256)
Mean (95% CI)	228 (202,254)	217 (183,250)
Min - Max	88 - 510	60 – 433
Clock-stop time		
Median (95% CI)	78 (53,93)	64 (35,84)
Mean (95% CI)	81 (65,98)	72 (52,91)
Min - Max	6 - 258	5 – 195
Active time		
Median (95% CI)	158 (145,176)	152 (148,178)
Mean (95% CI)	155 (144,166)	153 (138,170)
Min - Max	76 - 252	60 – 244

2. Outcome

An overview of the outcome of extensions of indications finalised in 2008 is presented in figure 8, together with a comparison with 2007.

Figure 8 Outcome of Extensions of Indications in 2007 and 2008



2.1 Positive CHMP opinions

Thirty-one out of 36 applications reached a positive opinion (86%), bringing new treatment options to patients. For a small subset of them (3/36), the positive opinion related to updates of the product information other than section 4.1 of the SPC ("therapeutic indications").

Positive CHMP opinions for medicinal products of notable public health interest

Zavesca (miglustat) is now indicated for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease. It is the first medicine to be approved for the treatment of Niemann-Pick type C disease, which is a rare disease in the European Union.

Velcade (bortezomib) is now indicated for the 1st line treatment of multiple myeloma in combination with oral melphalan and prednisone. This is a new treatment option for newly diagnosed, untreated patients with multiple myeloma who are not candidates for stem-cell transplantation.

Gardasil (human papilloma virus vaccine) and **Silgard** (human papilloma virus recombinant vaccine) are now indicated for the prevention of high-grade vaginal dysplastic lesions.

Two medicines had their use extended in the field of chronic infectious diseases:
- **Reyataz** (atazanavir) is now indicated for the treatment of patients with HIV and naïve of antiretroviral therapy.
- **Viread** (tenofovir) is now indicated for the treatment of chronic hepatitis B.

Two medicines had their use extended in the field of osteoporosis, providing more treatment options in particular for men:

- **Aclasta** (zoledronic acid), is now indicated for the treatment of osteoporosis in men at increased risk of fracture. Aclasta was already authorised for the treatment of osteoporosis in post-menopausal women.
- **Forsteo** (teriparatide) is now indicated for the treatment of osteoporosis associated with chronic glucocorticoid therapy in women and men at increased risk of fracture. Forsteo was already authorised for the treatment of osteoporosis in post-menopausal women and in men at increased risk of fracture.

Several medicines have received an approval to extend their use to paediatric patients:
- **Cancidas** (caspofungin acetate) for the treatment of severe fungal infections.
- **Enbrel** (etanercept), for the treatment of chronic severe plaque psoriasis in children from 8 years old, and who have had an inadequate response to previous therapy.
- **Apidra** (insulin glulisine) and **Optisulin** (insulin glargine) for the treatment of diabetes mellitus in children from 6 years old.
- **Humira** (adalimumab) for the treatment of active polyarticular juvenile idiopathic arthritis in adolescents aged 13 to 17 years old and who have had an inadequate response to previous therapy.

Positive CHMP opinions resulting in an update of the product information other than section 4.1 of the SPC ("therapeutic indications").

In 2008, 3 applications resulted in the inclusion of new clinical data in section 5.1 of the SPC:
- **Gardasil** (human papilloma virus vaccine) and **Silgard** (human papilloma virus recombinant vaccine), with respect to cross-protection against related non-vaccine human papillomavirus type disease.
- **Hepsera** (adefovir dipivoxil), with respect to treatment of adolescents aged 12 years old and over.
- **Remicade** (infliximab), with respect to reduced incidence of colectomy in patients with ulcerative colitis treated with Remicade.

Detailed information on CHMP positive opinions, with or without update of section 4.1 of the SPC, is available from the EPARs published on the EMEA webpage.

2.2 Negative CHMP opinions and withdrawals

The CHMP recommended 1 final negative opinion in 2008:

- **Cymbalta/Xeristar** (duloxetine), in the indication of fibromyalgia.

In addition, 4 applications were withdrawn prior to receiving a final CHMP opinion:

- **Evoltra** (clofarabine), an application for an extension of indication for treatment of acute myeloid leukaemia in elderly patients.

- **Invega** (paliperidone), an application for an extension of indication for treatment of acute manic episodes associated with bipolar I disorder.

- **Tygacil** (tigecycline), an application for an extension of indication for treatment of adult patients with community acquired pneumonia.

- **Taxotere/Docetaxel Withrop** (docetaxel), in the indication of treatment of patients with operable breast cancer whose tumours overexpress HER2 in combination with trastuzumab, with or without carboplatin. This application was withdrawn during re-examination procedure.

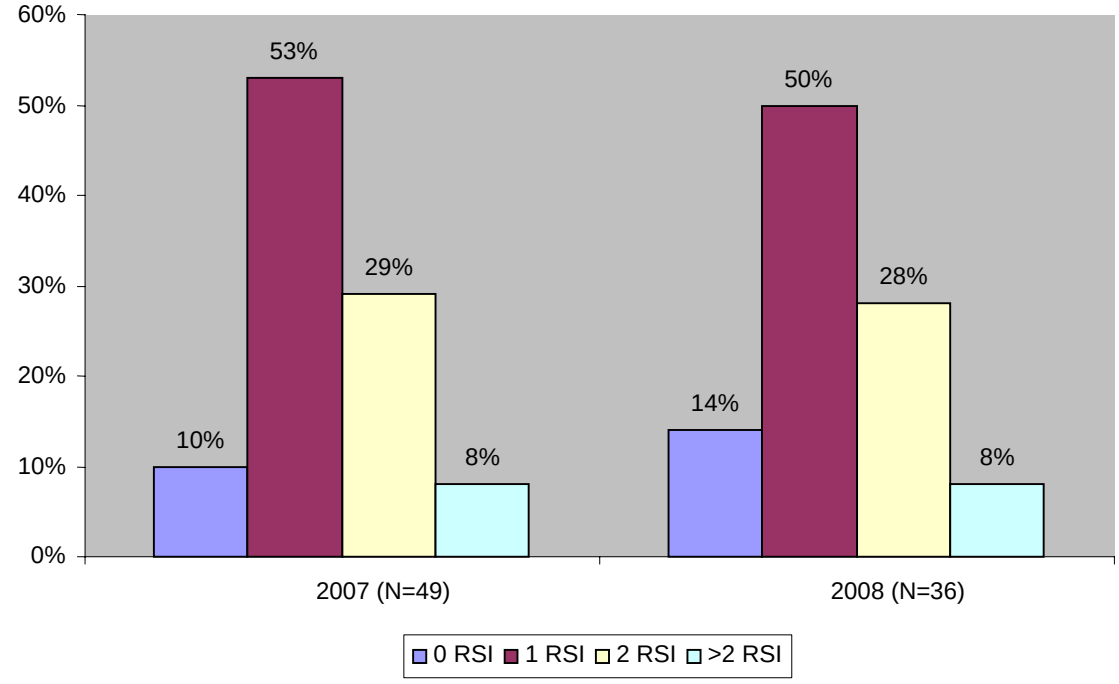
Detailed information on negative opinions and withdrawals is systematically published on the EMEA webpage (Questions and Answers and CHMP Assessment Report).

3. Requests for supplementary information, major objections and oral explanations

3.1. Requests for supplementary information (RSI)

As shown in figure 9, the number of RSI per procedure in 2008 is very similar to that of 2007. At least 1 RSI was adopted for most of the extension of indication procedures in 2008 (86%), and several procedures led to more than 2 RSIs (8%).

Figure 9. Number of RSIs per procedure in 2007 and 2008



3.2 Major objections (MO)

The proportion of procedures for which MOs were adopted continued to increase in 2008 (58%), compared to 2007 (51%). As shown in table 8, MOs contributed considerably to extend the review times.

Table 8. Mean and median values of the overall processing time, active review time and clock-stop time, with and without major objections in 2008.

	Major Objections N = 21		No Major Objections N = 14	
	Mean (95% CI)	Median (95% CI)	Mean (95% CI)	Median (95% CI)
Overall time	261 (221,300)	241 (216,342)	157 (111,203)	147 (88,279)
Active time	176 (158,193)	161 (153,212)	124 (101,148)	123 (88,180)
Clock-stop time	85 (61,110)	80 (59,130)	46 (14,78)	28 (18,N/A)

The influence of MOs on the review times appears to result primarily from a reduction of the review times for procedures without major objections, as the median review times for these procedures decreased considerably in 2008 compared to 2007. This is particularly true for clock-stop times (table 9). In contrast, the review times for procedures with MOs are very comparable in 2007 and 2008. Thus, marketing authorisation holders contributed to the granting of quicker approvals for the most straightforward procedures by responding more quickly to RSIs.

Table 9 Median values of the overall processing time, active review time and clock-stop time, with and without major objections in 2007 and 2008.

	Major Objections		No Major Objections	
	Median 2007 (95% CI)	Median 2008 (95% CI)	Median 2007 (95% CI)	Median 2008 (95% CI)
Overall time	251 (209,279)	241 (216,342)	216 (209,237)	147 (88,279)
Active time	167 (151,182)	161 (153,212)	152 (133,179)	123 (88,180)
Clock-stop time	84 (42,112)	80 (59,130)	67 (57,155)	28 (18,NA*)

* not available

3.3. Oral explanation

Only 2 applications out of 36 were subject to an oral explanation in 2008 (6%). This is relatively less than in 2007 (16%). For these 2 applications, the oral explanation did not allow solving the major concerns raised by the CHMP as one application resulted in a negative opinion, and the other in a withdrawal.

4. Scientific advisory groups (SAGs) and *ad-hoc* expert meetings

Two SAGs (1 oncology SAG and 1 Anti-infective SAG) were convened for extensions of applications in 2008 (6% of procedures). An *ad-hoc* expert group was also convened in 2008.

Overall, 9 SAGs and *ad-hoc* expert groups were convened during the review of extensions of indications finalised between the introduction of the SAGs mid 2005 and December 2008 (1 in 2006, 6 in 2007 and 2 in 2008): 3 cardiovascular, 2 anti-infectives, 1 diabetes/endocrinology, and 1 oncology SAG. This accounts for 6% of the extensions of indications finalised over the same period.

Scientific advisory groups and *ad-hoc* expert groups play an important role in the decision making process, by providing the CHMP with the position of experts on specific unresolved issues. For extensions of indications, SAG and *ad-hoc* expert groups are typically convened to assess the clinical relevance of data to the population applied for, or adequate sub-populations, in the context of a specific concern of the CHMP relating to safety, study methodology or the magnitude/consistency of efficacy data. The final procedure outcomes have always but in one occasion been consistent with recommendations given by the SAGs and *ad-hoc* expert groups.

5. Scientific Advice (SA)

In 2008, SA was given in relation to the sought new indication for 3 of the 36 procedures (8%), which is less than in 2007 (20%).

The small size of the sample in 2008 does not permit to draw definite conclusions on the potential impact of SA on the subsequent outcome of procedures, or on the concerns raised during the assessment. There was no significant association between prior SA and adoption of major objections (table 10), nor between prior SA and final outcome in 2008. However, such impact is complicated to assess, in particular for the following reasons:

- The allocation of the SA is not random as products with SA probably have most difficult/hazardous development
- An analysis on the level of adherence to the SA outcome is currently not available for extensions of indication, neither for MAHs nor for CHMP.

Table 10: $\chi 2$ test assessing the impact of prior Scientific Advise on subsequent Major Objection

	MO: Yes	MO: No	Total
SA+	2	1	3
SA-	19	14	33
Total	21	15	36

Degrees of freedom: 1; $\alpha = 0.05$
Calculated χ 2 value (0.09) < tabled χ 2 value (3.84)