European Medicines Agency

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# Survey 2007 on the performance of EMEA scientific procedures for medicinal products for human use

**Management Board**
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**Executive Summary**

Pre-authorisation

In 2007 there were sixty-eight applications with an outcome in the CHMP scientific evaluation; fifty-one with a positive outcome and seventeen (25%) with a negative outcome.

The clock-stop time appears to have been somewhat reduced since 2004 which may be due to better communication between the CHMP and the applicant around the time of the Day 120 List of Questions. In 2007, two applications (Isentress for HIV infection and Soliris for paroxysmal nocturnal haemoglobinuria) followed the accelerated assessment procedure and were approved within the stipulated 150 days. There were 4 applications that were initially accepted for accelerated review but then reverted to a normal timetable due to major outstanding issues that could not be resolved within the accelerated timetable. Besides being the first medicinal product for which an accelerated assessment procedure was concluded successfully, Soliris was also the first product submitted by a company benefiting from specific incentives for small and medium-sized enterprises (SMEs) to receive a positive opinion. In total there have been 7 products from SMEs with an outcome – all during 2007. Only one was approved whereas 3 were withdrawn prior to opinion, two received negative opinions after appeal and one withdrew after appeal.

Three products have received conditional marketing authorisations during 2007. They were in the areas of HIV infection and cancer. The marketing authorisation holders have committed to submit a number of specific obligations within defined timeframes that will be part of renewed assessments of the benefit risk balance by the CHMP.

There were nine orphan designated drugs that were approved in this period. The proportion of approved orphan designated drugs reached its highest peak in last years' review (24%) and was 18% of all approved products this year. This year, seven of the nine orphan drugs that received a positive opinion from the scientific committee belonged to the area of cancer/immunomodulator.

This year 2007, 34 (50%) of the 68 applications with an outcome were preceded by scientific advice which means that an increasing proportion of MAAs is preceded by SA. A specific analysis of the adherence to scientific advice for applications receiving scientific advice with an outcome during 2004 to November 2007 shows that adherence to SA may indeed be a contributory factor to a successful outcome.

Post-authorisation

In 2007, 49 applications (58 with duplicate applications included) for extensions of indications for centrally authorised products had an outcome in the CHMP scientific evaluation. Forty-six resulted in a positive opinion, 2 in a negative opinion, and 1 was withdrawn prior to opinion.

The overall processing time of extension of indication applications continued to increase in 2007. This appears to be primarily due to an increase in the clock-stop time. The proportion of applications concluded without request for supplementary information (RSI) grew compared to 2006. However, it is no longer exceptional to have more than 2 RSIs per application. The proportion of procedures with major objections continued to increase in 2007, and so did the use of scientific advisory groups meetings, ad-hoc expert meetings, and oral explanations. All together, these figures suggest increasingly complex assessments leading to longer review times.

Twenty percent of applications (10/49) were preceded by scientific advice (SA). No significant association was found between SA and subsequent applications outcome, but the sample size is limited.

The number of post-authorisation commitments remained high and comparable to 2006. A large number of these commitments related to pharmacovigilance issues. This may be partly explained by an increasing awareness and experience from industry and regulators on risk management and risk minimisation activities. Half of the opinions adopted for extension of indications included updated risk management plans.

## 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 aspects of outcomes of the scientific review of marketing authorisation applications and extensions in the CHMP, scientific advice/protocol assistance and orphan designations. Some aspects of public heath interest on approved new products are discussed.

This information will be made available on the EMEA webpage.

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### I. PRE-AUTHORISATION ACTIVITIES

### 1. Initial Evaluation of Applications for Marketing Authorisation

**Explanatory note:**
The EMEA Scientific Memory database has been used for these analyses. The data analysed encompasses applications with an outcome up to 31st December 2007.

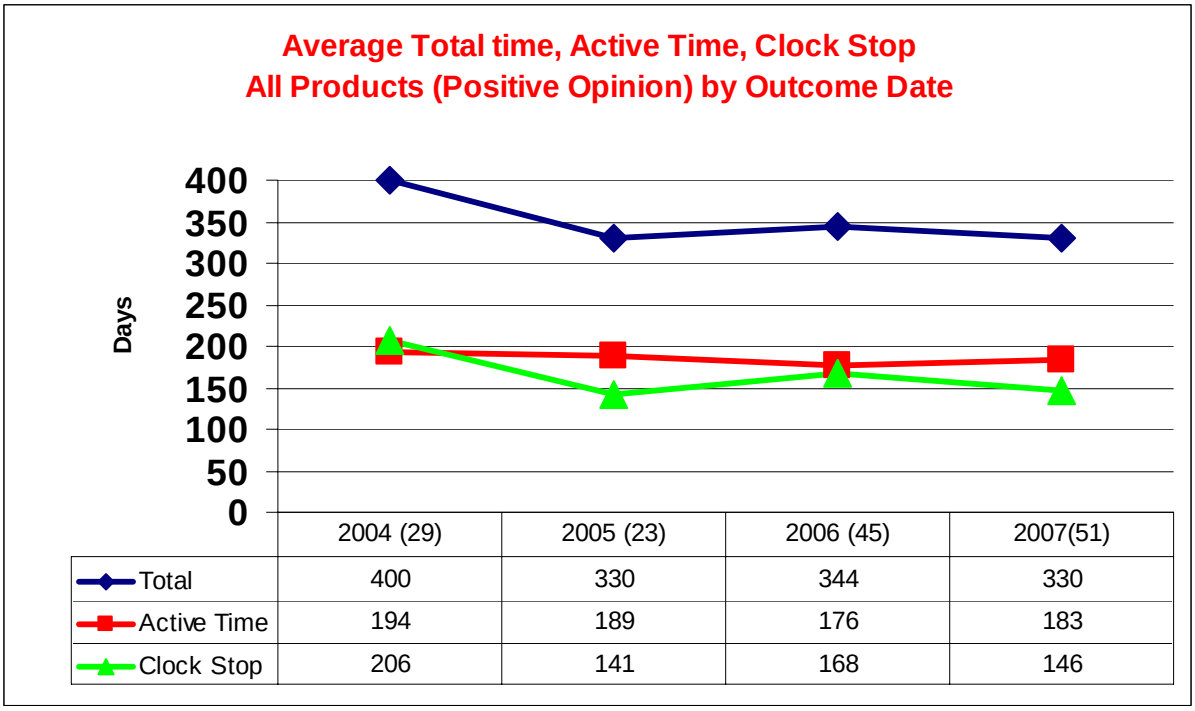
#### 1.1. Adherence to regulatory timelines and review times

Figure 1 show the review times for the applications that had a positive opinion during 2004, 2005, 2006 and 2007.
The overall review time in 2007 was about one year with the active time remaining within the stipulated 210 days and a clock-stop of about 150 days. The clock-stop time appears to have been somewhat reduced since 2004 which may be due to better communication between the CHMP and the applicant around the time of the Day 120 List of Questions. Debriefing meetings are regularly organised between the Rapporteur(s) and the applicant to clarify what sort of response would be expected to adequately respond to outstanding issues. Since ongoing applications are not included, there is a bias towards applications with shorter review times for the latter year.

Tables 1 and 2 in the annex describe the sixty-eight applications with an outcome in 2007. There were 10 applications that started their review already in 2004 or 2005 and had particularly long review times (these are highlighted in red in the tables in the annex). This is partly due to applications that had negative opinions re-examined following an appeal from the applicant on the negative opinion issued by the CHMP (table 2 in annex) but also applications where applicants needed extra long time to respond to the CHMP list of question.

Except for Isentress and Soliris (discussed below), there were no medicinal products that were approved within remarkably short review times (table 1 in the annex). Note that Tesavel, Orlistat and pioglitazone/metformin were informed consent applications. These types of applications require that reference has been made to an authorised medicinal product and that the holder of this marketing authorisation has given consent to the use of the dossier in the marketing authorisation procedure. Myfenax is a generic of Cellcept which has been authorised in the EU since February 1996.

**Figure 1**




| | 2004 (29) | 2005 (23) | 2006 (45) | 2007(51) |
|---|---|---|---|---|
| Total | 400 | 330 | 344 | 330 |
| Active Time | 194 | 189 | 176 | 183 |
| Clock Stop | 206 | 141 | 168 | 146 |

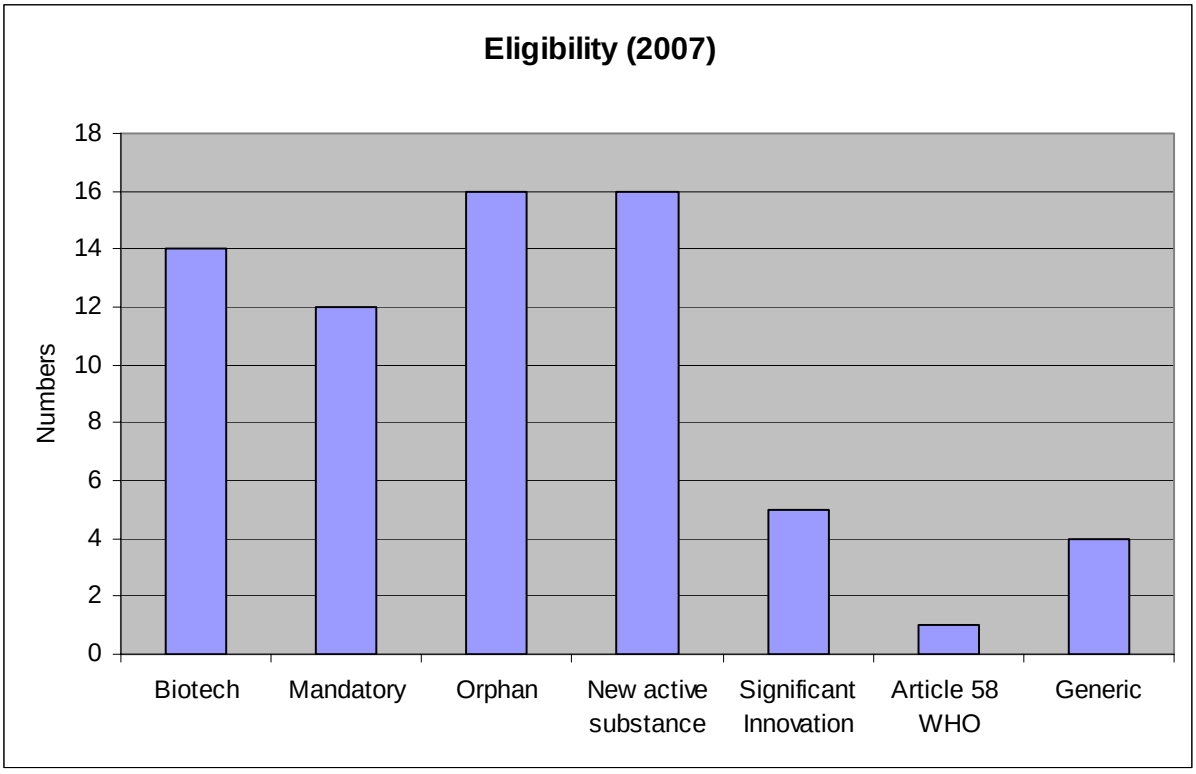
## 1.2. Outcomes of Marketing Authorisation Applications during 2007

There have been altogether sixty-eight MAA that have reached an outcome fifty-one with a positive outcome and seventeen with a negative outcome (tables 1 and 2 in the annex). These applications will be discussed from different aspects.

*Eligibility of applications*

Figure 2 shows that biotech products, orphan products and new active substances made up most of the sixty-eight medicinal products that were granted eligibility to the centralised procedure and had an outcome during 2007. The first generics to previous centrally approved products were also approved.

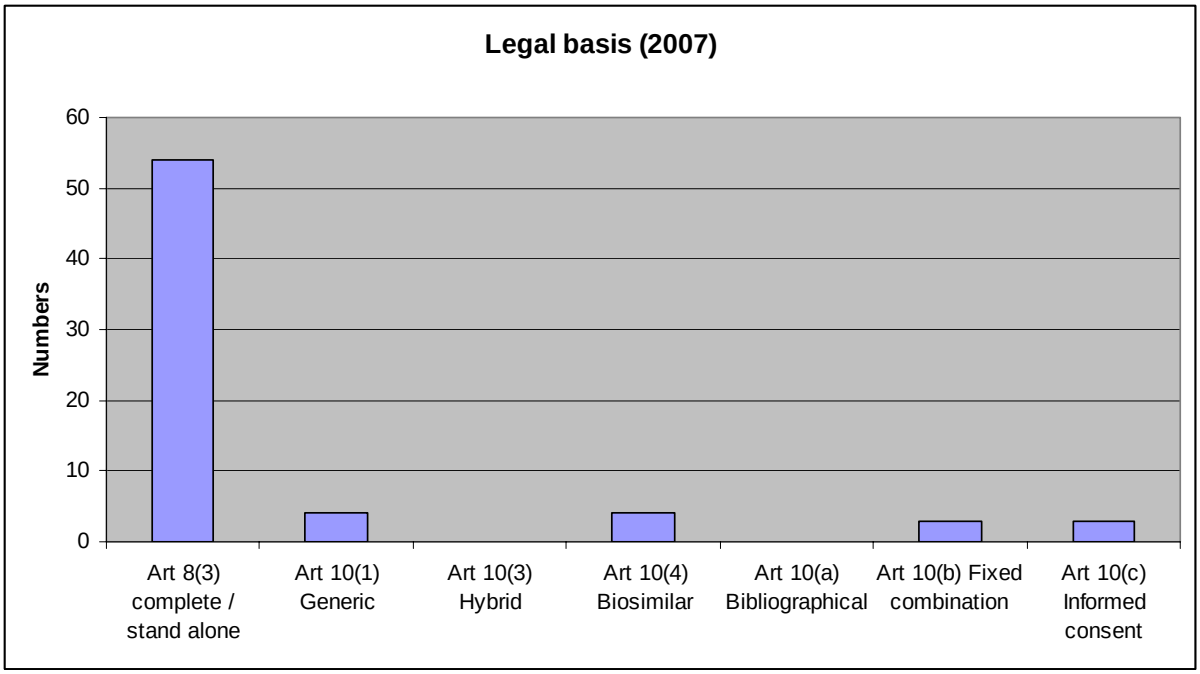
**Figure 2**




*Legal basis of applications*

Figure 3 shows that a majority of the sixty-eight applications with an outcome in 2007 were complete stand-alone applications.

**Figure 3**



*Products of public health interest*

Fifty-one of sixty-eight applications received a positive opinion by the CHMP during 2007. Except for three products (Januvia, Circadin and Tyverb), these were all approved following a consensus view in the Committee. As noted in last years' report, consensus views in the scientific committee are currently more prevalent than previously.

Table 1 in the annex describes the fifty-one applications that had a positive outcome during 2007. These products are grouped in accordance with the four different therapeutic groups managing applications in the preauthorisation unit of the EMEA. (These groups also manage applications outside their defined core areas).

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

Eculizumab (Soliris) is a designated orphan medicinal product, intended to reduce haemolysis (destruction of red blood cells) in patients with paroxysmal nocturnal haemoglobinuria, a rare blood disorder in which the red blood cells are weak and are thus destroyed more rapidly than normal, causing the urine to turn red or dark during an episode (or paroxysm) of haemolysis.

Human Papillomavirus vaccine [Types 16, 18] (Cervarix) is the second vaccine authorised for prophylaxis against high-grade cervical intraepithelial neoplasia (CIN grades 2 and 3) and cervical cancer causally related to Human Papillomavirus (HPV) types 16 and 18.

Celsentri (Maraviroc) and Raltegravir (Isentress) belong to new classes of anti-retroviral medicinal products (CCR5 inhibitors and Integrase inhibitors, respectively) and the benefits - when used in combination with other antiretroviral medicinal products - are their ability to reduce the amount of HIV in plasma (viral load) and to increase the number of T cells (specifically CD4 cells) treatment-experienced patients.

Pandemic influenza vaccines (Daronix, Focetria): These mock-up pandemic influenza vaccines are intended for the prevention of influenza during an officially declared pandemic situation. Marketing authorisations under exceptional circumstances were granted subject to certain specific obligations to be reviewed annually. A mock-up pandemic influenza vaccine is not intended for use or stockpiling. Based on the mock-up, a final vaccine can be prepared quickly in the event of a pandemic outbreak, once the responsible strain has been identified.

Lenalodimide (Revlimid) has a chemical structure that resembles that of thalidomide, a substance that was used in medicines in the late 1950s and early 1960s. It is now approved in multiple myeloma where it works by blocking the development of tumour cells and by stimulating some of the specialised cells of the immune system to attack the cancerous cells. Clinical studies have shown that Revlimid can prolong the time until multiple myeloma gets worse

Vectibix, (panitumumab) is a monoclonal antibody which binds to the epidermal growth factor receptor (EGFR), which can be found on the surface of certain tumour cells. As a result of this binding, the tumour cells can no longer receive the messages they need for growth, progression and spreading (metastasis). Vectibix is to be used to treat metastatic carcinoma of the colon or rectum.. Vectibix is to be used on its own after treatment with a combination of anticancer medicines that includes 5-fluorouracil, irinotecan or oxaliplatin has stopped working.

Tyverb (lapatinib) is a so-called protein-tyrosine kinase inhibitor that inhibits tumour cell growth by inhibiting the growth factor receptors EGFR and HER2. Tyverb is indicated, in combination with capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress HER2 and who have progressive disease following prior therapy. Such therapy must include anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting.

Vildagliptin (Galvus) and Sitagliptin (Januvia) are the first 2 DPP-IV inhibitors and are both indicated for type II diabetes. They work by enhancing endogenous incretin action. DPP-IV inhibitors are able to

lower blood glucose in a glucose-dependent manner; enhance beta-cell mass, and promote satiety, thereby reducing food intake and, subsequently, body weight.

Alsikeren (Rasilez) is the first renin inhibitor indicated for treatment of hypertension. It blocks the activity of a human enzyme called renin, which is involved in the production of a substance, angiotensin I, in the body. Angiotensin I is converted into the hormone angiotensin II, which is a powerful vasoconstrictor (it narrows blood vessels). By blocking the production of angiotensin I, levels of both angiotensin I and angiotensin II fall. This causes vasodilation (widening of the blood vessels), so that the blood pressure drops and the potential risk of damage caused by high blood pressure may be reduced.

*Products with accelerated approvals*

Accelerated assessment was introduced by the revised EU pharmaceutical legislation in November 2005. The aim of this new regulatory tool is to help speed up access of patients to new medicines of major public-health interest. Companies can request accelerated assessment provided they are able to demonstrate that their product responds to unmet medical needs or constitutes a significant improvement over the available methods of prevention, diagnosis or treatment of a condition.

In 2007, two applications (Isentress and Soliris) have followed the accelerated assessment procedure and were approved within the stipulated 150 days. As inferred from the annex, table 1, there were 4 applications that were initially accepted for accelerated review but then reverted to a normal timetable due to major outstanding issues that could not be resolved within the accelerated timetable.

Besides being the first medicinal product for which an accelerated assessment procedure was concluded successfully, Soliris was also the first product submitted by a company benefiting from specific incentives for small and medium-sized enterprises (SMEs) to receive a positive opinion.

*Products with conditional approvals*

The revised EU pharmaceutical legislation also provides a legal basis for a conditional marketing authorisation applying to medicinal products aimed at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases; medicinal products to be used in emergency situations, in response to public threats duly recognised either by the WHO or by the Community in the framework of Decision (EC) No 2119/98; medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000. Although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, all the following requirements are judged to have been met: the risk-benefit balance is positive; it is likely that the applicant will be in a position to provide the comprehensive clinical data; unmet medical needs will be fulfilled; the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

Three products (Isentress, Vectibix and Tyverb; table 1 in annex) have received conditional marketing authorisations during 2007. The marketing authorisation holders have committed to submit a number of specific obligations within defined timeframes that will be part of renewed assessments of the benefit risk balance by the CHMP.

*Article 58 opinions*

The European review of the Pharmaceutical Legislation in 2004 has introduced a new legal tool, so called "Article 58[1]", allowing medicinal products intending to be used in developing countries outside the EU to get scientific advice in drug development and/or a scientific review evaluation according to EU standards.

[1] Regulation (EC) No 726/2004 (31 March 2004), Article 58, OJ L 136, 30.4.2004, p.1, states that "The Agency may give a scientific opinion, in the context of cooperation with the World Health Organisation, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community. For this purpose, an application shall be submitted to the Agency in accordance with the provisions of Article 6. The Committee for Medicinal Products for Human Use may, after consulting the World Health Organisation, draw up a scientific opinion in accordance with Articles 6 to 9 [EU data requirements, Fees, Timetable etc…]. The provisions of Article 10 [Commission Decision granting a marketing authorisation] shall not apply".

"Article 58" Scientific Opinions thus responds to the need to protect public health and to give scientific assistance to non-EU member countries in the context of cooperation with the WHO.

At the same time this allows rapid access to those countries for important medicinal products often life saving, or medicines for diseases[2] or medical situations that does not exist in developed countries. It is also recognised that some countries can face difficulties in ensuring access to certain medicines due to the lack of regulatory capacity in particular for assessing products that have no marketing authorisation in developed countries.

The objective is to deliver a CHMP scientific opinion of equal standing to the opinions provided for medicinal products intended to be used/marketed in the EU, taking into consideration specificities of developing countries such as epidemiology, conditions of use etc. In order to achieve this objective, the procedure mirrors the EU centralised evaluation procedure in line with the legislation, and involves, European and WHO experts.

Since Article 58 provisions were made available, the EMEA has issued scientific opinions for three medicinal products intended for the treatment of AIDS. However, there were no products with such scientific opinions during 2007; one paediatric combined vaccine (Globorix) was withdrawn by the applicant.

*Products with negative outcomes (withdrawals and negative opinions)*

Seventeen (25%) of the sixty-eight applications with an outcome in this period received negative opinions from the Committee or were withdrawn by the applicants before the CHMP reached its opinion (table 2 in the Annex).

There were four applications that remained with a negative opinion (Genasense, Natalizumab and Mycograb) or were withdrawn (Cerepro) following CHMP re-examination of the first negative opinion, whereas the Vectibix opinion became positive after re-examination. In this case the CHMP adopted a positive opinion recommending the granting of a conditional marketing authorisation by majority (19 out of 29 votes) for Vectibix as monotherapy for the treatment of patients with EGFR expressing metastatic colorectal carcinoma with non-mutated (wild-type) KRAS after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan- containing chemotherapy regimens .

### 1.3. Marketing Authorisation Applications (MAAs) with Orphan status and Scientific Advice/Protocol assistance

*Proportion of MAAs with Orphan status*

Table 1 here and table 1 in the annex show that there were nine orphan designated drugs that were approved in this period. The proportion of approved orphan designated drugs reached its highest peak in last years' review (24%) and was 18% of all approved applications this year. This year, seven of the nine orphan drugs that received a positive opinion from the scientific committee belonged to the area of cancer/immunomodulators.

**Table 1:** Proportion of approved MAAs with orphan status of all approved MAAs

| | **2005** | **2006** | **2007** |
|---|---|---|---|
| **Orphan Drugs** | 3/23 (13%) | 11/45 (24%) | 9/51 (18%) |

[2] Such diseases are vaccines used or of possible use in the WHO Expanded Programme on Immunisation (EPI), vaccines for protection against a WHO public Health priority disease, vaccines that are part of WHO managed stockpile for emergency and medicinal products for WHO target disease such as HIV/AIDS, malaria, Tuberculosis, lymphatic filariasis, trachoma, leishmaniasis, schistosomiasis, African trypanosomiasis, onchocerciasis, dengue fever, Chagas disease, leprosy.

Table 2 below and table 2 in the annex shows that eight orphan designated drugs had a negative outcome in this period. This year orphan designated products make up almost 50% of all products with negative outcomes. Four of these (Cerepro, Iplex, Mycograb, and Voraxase) were from small and medium sized companies as discussed below.

**Table 2:** Proportion of Negative outcomes for orphan drugs of all MMAs with a negative outcome

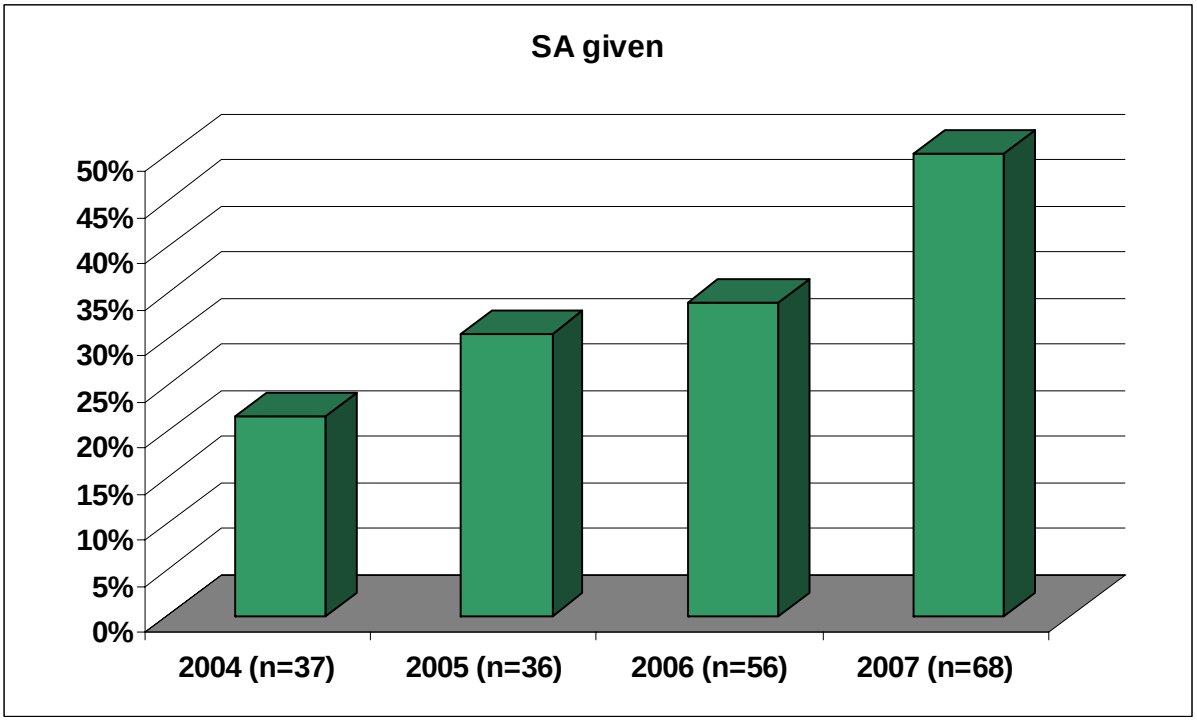
| | **2005** | **2006** | **2007** |
|---|---|---|---|
| **Orphan Drugs** | 5/13 (38%) | 4/11 (36%) | 8/17 (47%) |

*MAAs with Scientific Advice (includes protocol assistance)*

This year 2007 50% (34/68) of all applications with an outcome were preceded by SA (figure 4). Thus, an increasing proportion of MAAs is preceded by SA. Twenty-four (47%) of the 51 positive outcomes and 10/17(59%) applications with a negative outcome received SA prior to marketing authorisation application. This latter aspect is further discussed below.

Included in these figures are 12 (70%) out of the 17 orphan designated products that had protocol assistance before the marketing authorisation application.

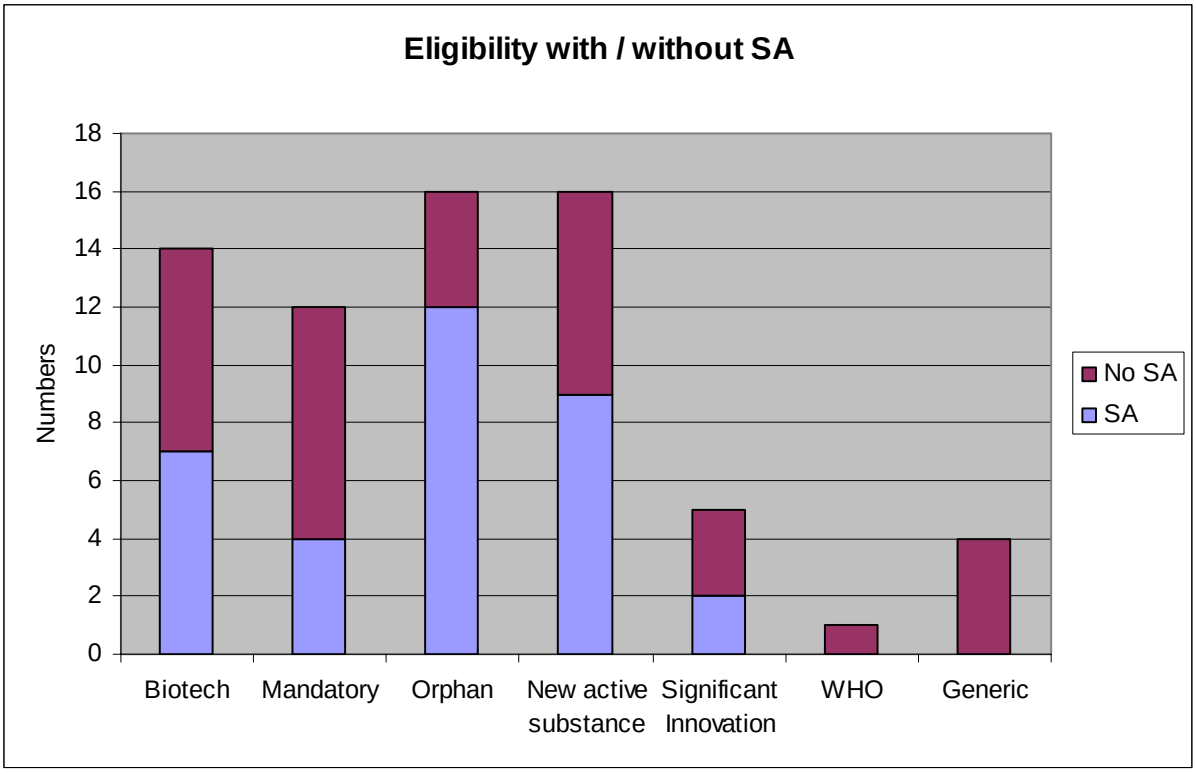
**Figure 4:** Proportion of MAAs that received SA – by outcome year




*Distribution of scientific advice over eligibility*

Figure 5 shows the numbers and distribution of SA over eligibility. The figure indicate that the highest proportion of scientific advice was given to orphan designated products (70%) followed by new active substances (56%), biotech products and mandatory scope (both 50%) and significant innovation (40%).

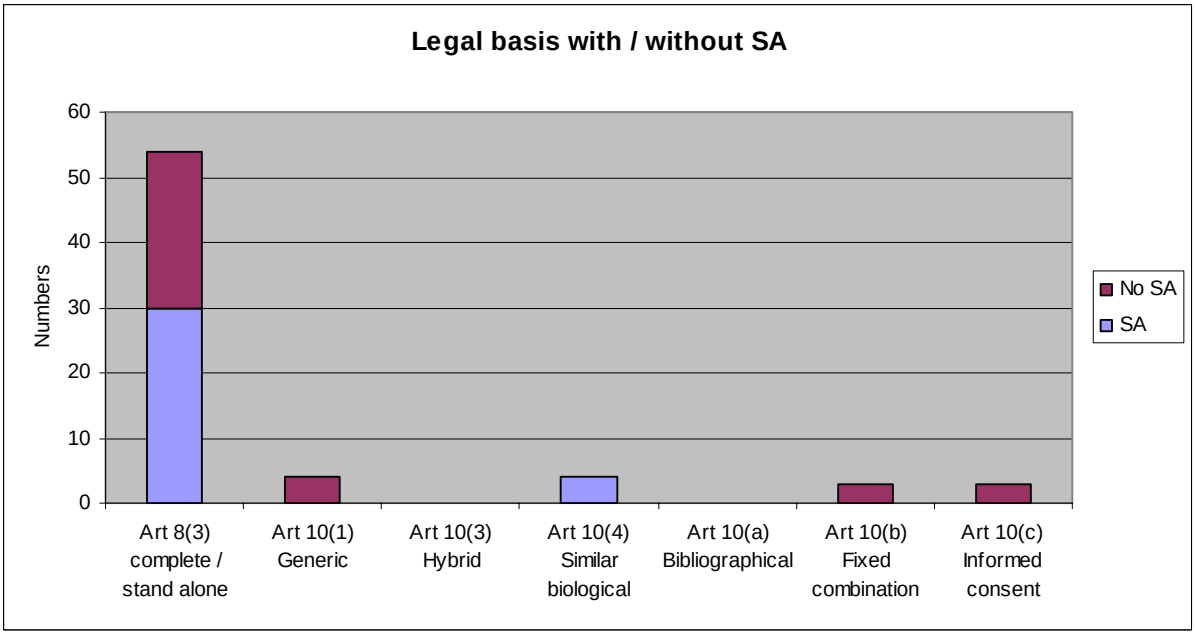
**Figure 5**




*Distribution of scientific advice over legal basis*

Figure 6 shows the number and distribution of SA over legal basis where notably all 4 similar biological applications had received prior SA.

**Figure 6**



*Impact of Scientific Advice (SA) on marketing authorisation applications*

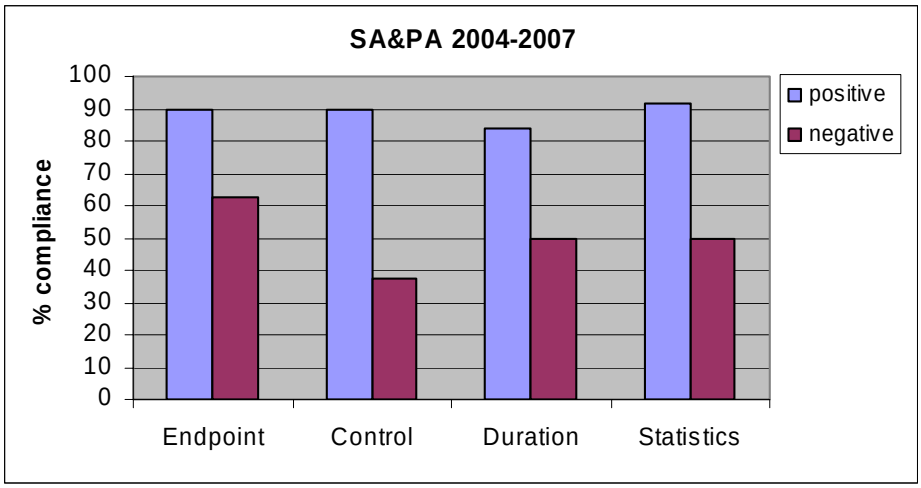
The objective of scientific advice is to advice on the drug development programme from an EU regulatory perspective. We have previously reported that there is an association between prior scientific advice and success of MAAs.

As mentioned above twenty-four (47%) of the 51 positive outcomes were preceded by scientific advice. There were ten/seventeen (59%) applications) with a negative outcome that had received SA prior to marketing authorisation application. This is not unusual and there are probably several reasons for this. The Applicant may chose to follow or not to follow scientific advice for different reasons as the case may be. Hence, the CHMP may during the critical review identify major objections to licensing of a new product even though scientific advice has been given in the past. These aspects are further analysed below (i,ii). Hence, a specific analysis of the adherence to scientific advice for applications receiving scientific advice with an outcome during 2004 to November 2007 indicates that adherence to SA may indeed be a contributory factor to a successful outcome. As could be expected, applications that adhered to the SA also appeared to have less major objections raised in the areas of previous scientific advice.

<u>Adherence to SA (including protocol assistance). Impact on success (i) and Major Objections at Day 120 (ii).</u>

(i) In a special analysis, comprising SA for applications with an outcome during 2004 until November 2007, an attempt to measure adherence was made by investigating compliance with CHMP scientific advice given on choice of primary endpoint, choice of comparator, study duration and statistical analysis. If the clinical study in the MAA that had been subject to the scientific advice complied with the SA as judged from the EPAR, the SA was considered to have been adhered to. Thus, adherence/compliance with SA could be evaluated in 45 applications with positive opinions and 14 with negative outcomes. Figure 7 indicates that the adherence/compliance with the SA was higher for those with positive outcomes (blue bars) than for those with negative outcomes (red bars) for all items studied (statistically significant for “control, P=0.0056). It would therefore seem as if adherence with SA is associated with higher chances of success.

**Figure 7**




(ii) As a consequence of the findings above one would expect that the CHMP would raise less major objections on applications that had complied with the CHMP scientific advice than on applications that did not follow the SA. This was considered by investigating those applications that had a SA on any of the defined aspects (comparator, endpoint, duration of trial, and statistics/analysis) as to whether a major objection on that aspect was raised or not at ay 120 of the CHMP assessment.
Table 3 shows the proportion of applications with defined major objections and whether a SA had indeed been given on that aspect. There was one application out of 25 that followed the SA given on comparator design issues that still had a major objection on this aspect at day 120. The same application was also the one of the 31 applications that followed the SA on choice of endpoints but still had major objections related to the choice of endpoints. In this cancer product, the endpoint was already criticized at the SA level but not totally rejected, whereas the comparator was accepted. However the CHMP raised major objections on those aspects at Day 120.
Major objection related to the way the data are analysed are quite frequent and it is quite "normal" that the CHMP raises the need for alternative analysis to be performed by the applicant when the data are available in order to ensure the robustness of information. This was indeed the case in 2 of the 4 applications that had followed scientific advice on this aspect. In these cases the issue could not have been foreseen at the time of SA. However, in the third case there was a major objection related to the "unexpected" appearance of an interim analysis in the application. This interim analysis was never discussed at the time of SA and was insufficiently substantiated in the application. In the 4$^{th}$ case the non-inferiority margin was agreed and followed by the applicant but data failed to meet with this margin. The applicant performed an alternative analysis of the data that was not accepted by the CHMP, who wanted additional justifications. Trial duration was raised as a major objection in only one case where SA had not been followed and which eventually faced negative outcome primarily based on concerns over the consistency of the treatment effect

In summary, only 7% (6/92) of those SA that were followed had major objections as opposed to 59% (16/27) of those that did not follow the SA on these aspects. It thus seems that a clearly lower proportion of major objections were raised on applications judged as adhering to SA as opposed to those judged not to have followed SA

**Table 3:** Proportion of applications with Major Objections on MAAs that followed/not followed defined SA

| SA/Major Objections | Comparator/design | Endpoint | Statistics/analysis | Trial duration | Total |
|---|---|---|---|---|---|
| SA Followed (Green in Fig above) | 1/25 | 1/31 | 4/12 | 0/24 | 6/92 (7%) |
| SA Not followed (Red in Fig above) | 9/13 | 4/5 | 2/3 | 1/6 | 16/27 (59%) |

### 1.4. Marketing Authorisation applications) from Small and Medium Sized Companies (SMEs)

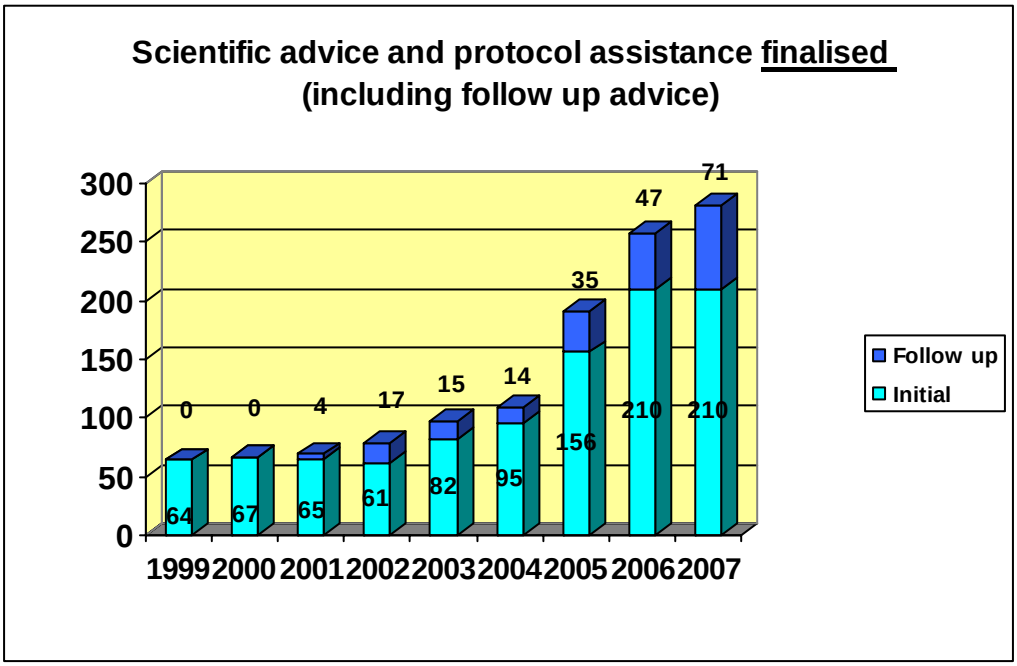
Since the start of SME initiative, twenty-three SME companies have submitted marketing authorisation applications, 20 for human medicinal products and 3 for veterinary medicinal products. One medicinal product for human use (Soliris) and one for veterinary use (Rheumocam) have gone on to receive a marketing authorisation. In total there have been 7 products from SMEs with an outcome – all during 2007. Only one (Soliris) was approved whereas 3 (Gastromotal, Voraxaze and Iplex) were withdrawn prior to opinion, two (Genasense and Mycograb) received negative opinions after appeal and one (Cerepro) withdrew after appeal (tables 1 and 2 in the annex). All other applications are currently under review.

## 2. Applications for CHMP Scientific Advice/Protocol Assistance

The marked increase in the numbers of SA/PA was sustained in 2007. A further small increase from 257 to 281 procedures was even observed (Fig. 8). During 2007 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.

- According to the new procedure the presubmission meetings had been enriched with the involvement of more scientific input from the CHMP experts. This was very much appreciated as shown by the number of presubmission meeting which was increased from 50 in 2006 to 124 in 2007
- The new stream-lined procedure of 40 or 70 days could be followed with only 19 exceptions out of 281 procedures
- The CHMP received 2 requests for broader and more general advice for specific types of medicinal products or treatments as compared to 1 request in 2006.
- A significant number of SA requests on acceptability of the development programme for conditional marketing authorisation (12 requests in 2006, 20 requests in 2007) and the development programme for marketing authorisation application under exceptional circumstances (2 requests in 2006, 6 requests in 2007) were also being handled.
- The definition of the follow-up procedure had been widened in the new framework 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. This was appreciated as shown by the percentage of follow-up in the overall procedures which increased from 47 in 2006 to 71 in 2007.
- 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. In 2007 the CHMP received a high number of SA/PA requests discussing alternative clinical trials designs, e.g. flexible/adaptive designs which are aimed to speed up development. Based on this interest the CHMP/SAWP organised together with EFPIA a large meeting involving all stakeholders to discuss alternative clinical trial designs and their regulatory acceptability.
- 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. This is different from the “classical” SA provided so far. The EMEA secretariat together with the CHMP and SAWP chairs and several CHMP members have been working in 2007 for the development of a new procedure for this purpose which will be further developed and published in 2008.

**Figure 8**




### 3. Applications for Orphan status

*Number reviewed and adherence to regulatory timelines*

Table 4 shows the number of applied and approved designations for orphan medicinal products, which has consolidated the trend seen in the past three years and amounted to 125 applications. Only one negative opinion was adopted in 2007. The average time to COMP opinion and Commission decision was 65 and 44 days, respectively. Last year the figures were 57 and 25 days, respectively.

**Table 4:** Number of products that have received orphan designation 2005 and 2006.

| **Orphan Medicinal Product Procedures** | **2006** | **2007** |
|---|---|---|
| Applications for orphan medicinal product designation | 104 | 125 |
| Withdrawals | 20 | 19 |
| COMP opinions (positive) | 81 | 97 |
| Designation EC Decision | 80 | 94 |

As indicated in figure 9, oncology represents more than 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.

**Figure 9:** Therapeutic areas for positive COMP opinions in 2007

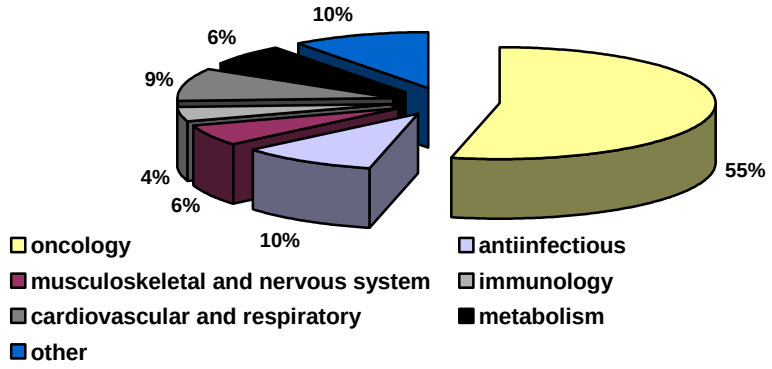
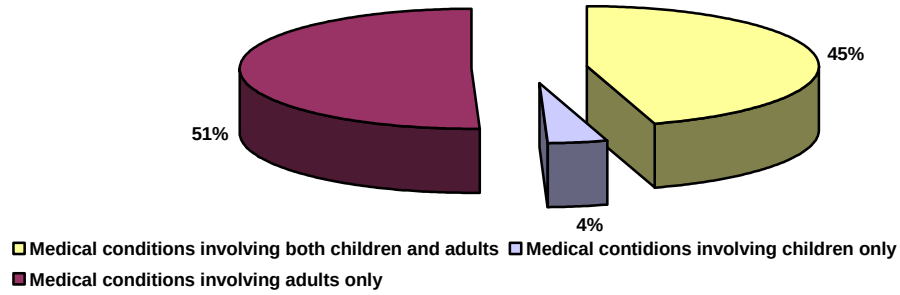



**Figure 10:** Orphan medicinal products for the treatment of adults and children 2007




In addition, it could be mentioned that prior to marketing authorisation it has to be established that products designated as orphans still fulfil the designation criteria This is necessary for these products in order to keep the orphan status once marketing authorisation is granted (Article 5 (12)(b) of Regulation 141/2000]. The review of the designation criteria is done by the COMP. In 2007 the COMP adopted 11 opinions on the fulfilment of the designation criteria prior to marketing authorisation.

## 4. Applications for SME status

Since the EMEA introduced provisions for SMEs in December 2005, 339 companies have submitted SME declarations to the agency. Of those: 246 currently have SME status assigned by EMEA. The large majority of companies are developing medicinal products for human use, 9 are veterinary companies, 8 companies are developing products for both human and veterinary use and 19 are regulatory consultants.

In 2007, the number of companies requesting SME status from the agency increased by 40% compared to the previous year. The number of renewal requests increased 3-fold compared to 2006. The innovation[3] profile of the assigned companies has been found to be very high (65%). Looking at the types of product under development, the broad breakdown into chemical entities vs. biologics is 37% and 58%

[3] Innovation, as defined in the survey, comprised therapeutic innovation (e.g., new target disease, new mechanism of action, new compound types, new treatment modalities), technical innovation (e.g. new delivery methods/formulation, new manufacturing techniques, nanotechnology) and scientific innovation (e.g. new research and development methods/tools, pharmacogenomics, biomarkers).

respectively. Although the large majority of companies are yet to place a product on the market, just over half have reached the clinical phase of development – with some 21% in late phase clinical trials.

Forty-six (46) SME companies requested scientific advice from the agency in 2007, almost double that seen in 2006 (25).

# ANNEX

**Outcomes of marketing authorisation applications during 2007 - EMEA Preauthorisation unit.**

**Table 1**: Applications (n=) with a positive opinion by outcome year 2007.
**Table 2**: Applications with a negative outcome during 2007

**Table 1:** Applications (n= 51) with a positive opinion during 2007.

| INN (Brand name) | Therapeutic Area | Paediatric indication | SA | Active Time | Clock Stop |
|---|---|---|---|---|---|
| | "ANTIINFECTIVES" | | | | |
| Epoetin alfa*, (**Abseamed, Binocrit, Hexal**) | Anaemia of renal origin | Yes | Yes | 205 | 244 |
| Methoxy polyethylene glycol-epoetin beta * (**Mircera**) | Anaemia of renal origin | No | No | 176 | 189 |
| Epoetin Zeta **(Silapo**) | Anaemia associated with chronic renal failure | No | Yes | 202 | 254 |
| Advagraf (**Tacrolimus**) | Transplant rejection | No | No | 201 | 87 |
| Altargo **(Retapamulin**) | Superficial skin infections | Yes | Yes | 191 | 55 |
| Maraviroc *, *** **(Celsentri**) | HIV infection | No | No | 169 | 35 |
| Efavirenz/emtricitabine/tenofovir disoproxil fumarate (**Atripla**) | HIV infection | No | No | 202 | 156 |
| Inactivated pandemic strain. Whole virion ***;***** (**Daronix**) | Pandemic Influenza | No | No | 142 | 174 |
| Anidulafungin (**Eccalta**) | Invasive Candidiasis | No | No | 210 | 85 |
| Abatacept * (**Orenci**a) | Active rheumatoid arthritis | No | No | **204** | **245** |
| H5N1 virus surface inactivated antigen ***; ***** (**Focetria**) | Pandemic Influenza | No | Yes | 162 | 224 |
| Human papilloma virus (**Cervarix**) | Prevention of high-grade cervical intraepithelial neoplasia (CIN grades 2 and 3) and cervical cancer causally related to Human Papillomavirus (HPV) types 16 and 18. | Yes | Yes | 202 | 275 |
| Human normal immunoglobin (IVIg) (**Flebogammadi**f) | Replacement therapy in Primary immunodeficiency syndromes etc | No | No | 177 | 90 |
| Influenza vaccine (cell culture)*** (**Optaflu**) | Prophylaxis of influenza for adults (seasonal) | No | Yes | 202 | 79 |
| Telbivudine **(Sebivo**) | Chronic hepatitis B | No | No | 210 | 148 |

| INN (Brand name) | Therapeutic Area | Paediatric indication | SA | Active Time | Clock Stop |
|---|---|---|---|---|---|
| Raltegravir ***, **** **(Isentress)** | HIV infection | No | Yes | 141 | 35 |
| | " CNS" | | | | |
| Melatonin* (**Circadin**) | Primary insomnia | No | Yes | **209** | **338** |
| Paliperidone (**Invega**) | Adult schizophrenia | No | Yes | 202 | 135 |
| Fesoterodine **(Toviaz**) | Treatment of overactive bladder | No | No | 210 | 120 |
| Olanzapin **(OlanzapineNeopharma)** | Schizophrenia | No | No | 205 | 127 |
| Olanzapin (**Olanzapine Teva**) | Schizophrenia | No | No | 177 | 118 |
| Olanzapin (**Zalasta**) | Schizophrenia | No | No | 177 | 90 |
| Lyophilisate (**Cyanokit**) | Intoxication - hydrocyanic acid | No | No | 177 | 90 |
| Nepafenac (**Nevanac**) | Pain and inflammation associated with cataract surgery | No | No | 205 | 62 |
| | "ONCOLOGY" | | | | |
| Paclitaxel (**Abraxane**) | Metastatic breast cancer | No | Yes | 202 | 184 |
| Nelarabine *,**, ***** (**Atriance**) | T-cell lymphoma/T-cell acute leukaemia | Yes | Yes | 203 | 162 |
| 5-aminolevulinic hydrochloride **; **(Gliolan)** | Visualisation of malignant tissue during surgery for malignant glioma | No | Yes | 199 | 194 |
| Nilotinib **; (**Tasigna**) | Philadelphia chromosome positive chronic myelogenous leukaemia | No | Yes | 200 | 130 |
| Gadoversetamide (**Optimark**) | Magnetic resonance imaging | Yes | Yes | 196 | 169 |
| Lenalidomide ** (**Revlimid**) | Multiple Myeloma | | Yes | 199 | 159 |
| Eculizumab **;*** **(Soliris**) | Paroxysmal nocturnal hemoglobinuria | No | Yes | 147 | 36 |
| Trabectedin **;***** (**Yondelis**) | Advanced soft tissue sarcoma | No | No | 210 | 127 |
| Temsirolismus ** **(Torisel**) | Renal cell carcinoma | No | Yes | 203 | 127 |
| Panitumumab *, **** (**Vectibix**) | Metastatic carcinoma of the colon or rectum after failure of standard chemotherapy | No | No | 204 | 161 |

| INN (Brand name) | Therapeutic Area | Paediatric indication | SA | Active Time | Clock Stop |
|---|---|---|---|---|---|
| Fosaprepitant (**Ivemend**) | Prevention of chemotherapy-induced nausea and vomiting | No | No | 197 | 343 |
| Lapatinib *, **** (**Tyverb**) | Breast cancer | No | Yes | 202 | 212 |
| Mycophenolate mofetil (**Myfenax**) | Prophylaxis of acute transplant rejection | Yes | No | 138 | 8 |
| "ENDOCRINOLOGY/CARDIOVASCULAR" | | | | | |
| Mecasermin **; ***** **(Increlex)** | Primary Insulin-like Growth Factor Deficiency | Yes | No | **208** | **304** |
| Hydroxycarbamide ** **(Siklos**) | Vasoocclusive crises in Sickle Cell Syndrome | Yes | No | **208** | **339** |
| Orlistat GSK (**Orlistat**) | Obesity | No | No | 60 | 0 |
| Vildagliptin (**Galvus**) | Type II diabetes mellitus | No | Yes | 203 | 134 |
| Sitagliptin **(Januvia**) | Type II diabetes mellitus | No | Yes | 202 | 99 |
| Follitropin alfa and lutropin alfa (**Pergoveris**) | Stimulation of follicular development in patients with severe LH and FSH deficiency | No | No | 117 | 110 |
| Aliskiren (**Rasilez)** | Hypertension | No | Yes | 194 | 73 |
| Vildagliptin plus metformin hydrochloride **(Eucreas**) | Type 2 diabetes mellitus | No | No | 177 | 62 |
| Pioglitazone/metformin | Type 2 diabetes mellitus | No | No | 59 | 0 |
| Desloratadine, pseudoephedrine (**Aerinaz**e) | Seasonal allergic rhinitis | No | No | 196 | 85 |
| Fluticasone furoate *, (**Avamys**) | Seasonal and perennial allergic rhinitis | Yes | Yes | 202 | 226 |
| sitagliptin phosphate monohydrate **(Tesavel**) | Type 2 diabetes mellitus | No | No | 60 | 0 |

* Oral explanation; **Orphan medicinal product; *** Initial Accelerated assessment (means that it may have reverted to a normal timetable;**** Conditional marketing authorisation;*****Marketing authorisation under exceptional circumstances.
Red colour indicates products already submitted in 2004 or 2005

**Table 2:** Applications (n=17) with a negative outcome during 2007

| Product | Therapeutic Area | Paediatric indication | SA | Active Time | Clock Stop |
|---|---|---|---|---|---|
| "Antiinfectives" | | | | | |
| Efungumab **;*****; ****** (**Mycogra**b) | Invasive candidiasis | No | Yes | **207** | **391** |
| Garenoxacin mesylate *** (**Garenoxacin**) | Treatment of Infections | No | No | 117 | 27 |
| DTwP-HBV plus HibhenAC PRP-TT, MenC-TT and MenA-bTT conjugates *** **(Globorix)** | Combined Diphtheria, tetanus, pertussis (whole cell), Hepatitis B (rDNA), haemophilus | Yes | No | 120 | 87 |
| Natalizumab ** (**Natalizuma**b) | Chrohn's disease | No | Yes | **204** | **800** |
| Certolizumab pegol *, ***** **(Cimzia)** | Chrohn's disease | No | No | 202 | 238 |
| "CNS" | | | | | |
| Ovine hyaluronidase *** **(Vitragan**) | Treatment of vitreous haemorrhage | No | No | **117** | **201** |
| Flucinolone acetonide***;****** **(Retisert)** | Chronic non-infectious uveitis | No | Yes | 117 | 147 |
| rhC1INH *, ****** **(Rhucin)** | Oedema in patients with hereditary angioedema | No | Yes | 176 | 308 |
| Eprodisate disodium *, ****** **(Kiacta)** | Amyloidosis | No | Yes | 202 | 240 |
| "ONCOLOGY" | | | | | |
| Adenovirus-mediated HSV thymidine kinase gene ****, *****, ****** **(Cerepro)** | Operable high-grade malignant gliomas | No | Yes | **175** | **207** |
| Glucarpidase ***; ****** **(Voraxaze)** | Methotrexate toxicity | Yes | No | **177** | **465** |
| Oblimersen sodium **; ***** **(Genasense)** | Advanced malignant melanoma | No | No | 105 | 85 |
| Gemtuzumab ozogamicin *;*****;****** (**Mylotarg)** | CD33-positive Acute Myeloid Leukaemia in first relapse | No | Yes | **200** | **431** |

| Product | Therapeutic Area | Paediatric indication | SA | Active Time | Clock Stop |
|---|---|---|---|---|---|
| 13C-octanoic acid ***;***** **(Gastromotal)** | In vivo diagnosis of gastric emptying rate | No | Yes | 193 | 337 |
| Ferumoxtran * **(Sinerem)** | Diagnosis of lymph node metastases | No | Yes | 173 | 221 |
| “ENDOCRINOLOGY” | | | | | |
| Ruboxistaurin *** **(Arxxant)** | Diabetic retinopathy | No | Yes | 117 | 29 |
| Mecasermin ***;****** **(Iplex)** | Primary growth hormone insensitivity and growth hormone (GH) gene deletion with neutralising antibodies to GH | Yes | No | 117 | 29 |

* Negative opinion;** Negative opinion after appeal;***Withdrawn before opinion;**** Withdrawn after appeal; ***** Oral explanation;******Orphan designated medicinal product; ******* Initial Accelerated assessment (Means that it may have reverted to a normal timetable); ******** Conditional marketing authorisation; *********Marketing authorisation under exceptional circumstances. Red colour indicates products already submitted in 2004 or 2005.

## 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 2007. For information on other Post-Authorisation procedures conducted in 2007 (Other Type II variations, Type I variations, Renewals, Annual-reassessments, follow-up measures/specific obligations, and PSURs), please refer to the EMEA Annual Report 2007.

Although the Scientific Memory Database is not yet operational for Post-Authorisation procedures, dedicated tracking systems were used for the various analyses below.

In 2007, the CHMP reviewed 58 applications for extensions of indications for centrally authorised products (CAPs). Nine of the applications were for duplicate products. Therefore, 49 applications were taken into account in the various analyses performed and presented below.

Forty-six out of the 49 applications reached a positive opinion. The CHMP recommended 2 negative opinions, and 1 application was withdrawn prior to opinion.

In addition, 1 opinion was adopted for a product indicated for the treatment of Human Immunodeficiency Virus (HIV), and authorised under Article 58 of Regulation (EC) No 726/2004 (WHO cooperation).

### 1. Review times

The overall, active and clock-stop times for 2006 and 2007 are presented in figure 11 and summarised in table 5. These correspond to the time required to reach the first CHMP opinion (or the withdrawal of the application by the MAH). The extra time allocated for re-examination procedures is excluded from this analysis.

In 2007, the median overall processing time continued to increase, exceeding 220 days. The review time varies considerably amongst procedures, from 88 to 510 days. Review time is short when no request for supplementary information (RSI) is adopted during the procedure. In 2007, this was the case for 5 applications which were finalised within 90 days. However, as the variation regulation allows for multiple review periods of 90 days within the same procedure, the review of applications can become long due to the number and complexity of RSIs.

The median clock-stop time increased sharply in 2007 compared to 2006. The median active review time increased as well but to a lesser extent, indicating that the increased overall processing time is primarily due to longer clock-stops.

**Figure 11:** Kaplan Meier estimate of the overall (overall time equals active review time plus clock-stop time), active and clock-stop times for 2006 and 2007.

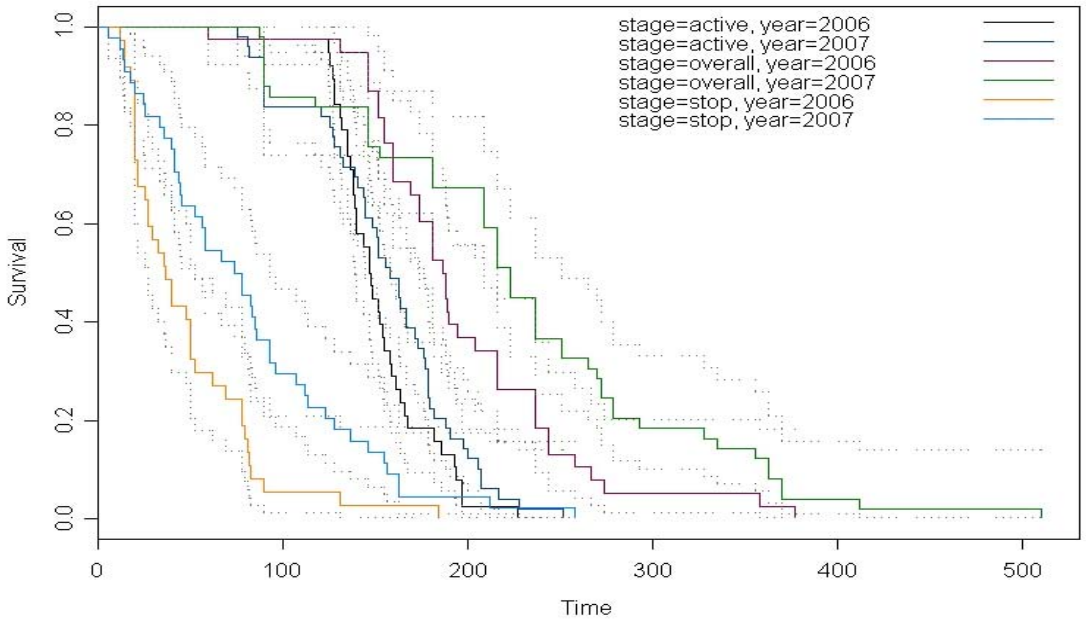



**Table 5:** Overview of overall, active and clock-stop times for 2006 and 2007

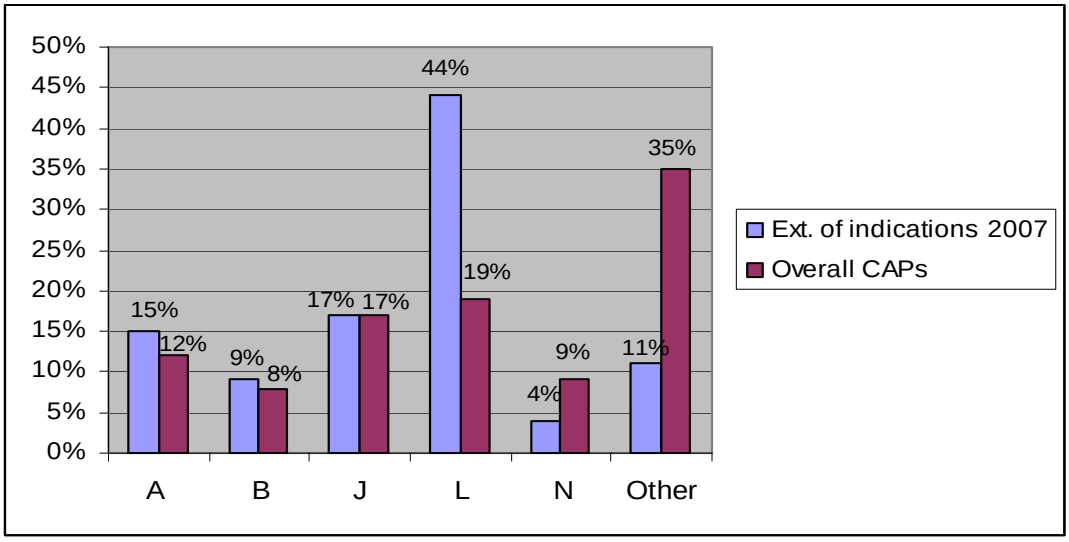
| | **2006** | **2007** |
|---|---|---|
| **Overall processing time (N=49)** | | |
| Median (95% CI) | 188 (174,216) | 223 (209,251) |
| Mean (95% CI) | 197 (178,217) | 228 (202,254) |
| Min - Max | 60 - 377 | 88 - 510 |
| **Clock-stop time (N=44)** | | |
| Median (95% CI) | 37 (27,53) | 78 (53,93) |
| Mean (95% CI) | 48 (36,60) | 81 (65,98) |
| Min - Max | 12 - 184 | 6 - 258 |
| **Active time (N=49)** | | |
| Median (95% CI) | 148 (139,159) | 158 (145,176) |
| Mean (95% CI) | 152 (142,161) | 155 (144,166) |
| Min - Max | 60 - 227 | 76 - 252 |

## 2. Outcome

- *Positive opinions*

Forty-six out of the 49 applications reached a positive opinion (94%). As in 2006, the majority of the new indications related to anti-cancer agents. New indications were also approved in the fields of diabetes, cardiovascular, infectious diseases, rheumatoid and inflammatory-bowel diseases, and central nervous system disorders (figure 12).

**Figure 12:** Distribution of Extensions of indications with positive CHMP opinion per ATC code vs. overall distribution of CAPs (A = Alimentary tract and metabolism; B = Blood and blood forming organs; J = Anti-infective for systemic use; L = Antineoplastic and immuno-modulating agents; N = Nervous system)




Opinions with particular significant interest from a public health point of view:

**Xeloda** (capecitabine) is now indicated for the 1st line treatment of advanced gastric cancer, and is the first oral chemotherapy approved in this indication. Xeloda was also granted a new indication for the treatment of metastatic colorectal cancer.

**Avastin** (bevacizumab), first in class angiogenesis inhibitor (authorised in 2005 for the treatment of colorectal carcinoma), is now authorised for the 1st line treatment of several other cancers: metastatic breast cancer; unresectable advanced, metastatic or recurrent non-small cell lung cancer; advanced and/or metastatic renal cell cancer.

**Januvia/Xelevia** (sitagliptin), first in class gliptin product (authorised in March 2007 for the treatment of Type II diabetes in dual therapy with metformin or PPAR agonists), is now authorised in dual oral therapy with a sulphonylurea. Its indication was also broadened in 2007 to triple oral therapy with metformin and sulfonylurea.

**Glustin** (pioglitazone) indications were also extended to the triple oral therapy, but also to the combined use with insulin (The same extensions of indications were already granted for the duplicate product Actos in 2006). Of note, in 2007, the CHMP lifted the contra-indication for the combined use of PPAR agonists with insulin for all the products of the class.

**Tracleer** (bosentan) is now indicated for the reduction of the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease, an orphan disease in the European Union.

**Nexavar** (sorafenib) is now indicated for the treatment of hepatocellular carcinoma, another orphan disease in the European Union.

**Xyrem** (sodium oxybate) was authorised in 2005 for the treatment of cataplexy in adult patients with narcolepsy. This indication was broadened in 2007 to encompass the full narcolepsy syndrome, an orphan disease in the European Union.

**Remicade** (infliximab) is now the first immunomodulator indicated in the treatment of severe active Crohn's disease in children and adolescents aged 6 to 17 year old.

**Aranesp/Nespo** (darbepoetin alfa) is now authorised for the treatment of anaemia associated with chronic renal failure in patients less than 11 year old.

**Combivir** (lamivudine/zidovudine) is now indicated for the ttreatment of HIV in paediatric patients weighing at least 30 kg. The product was previously authorised only for patients over 12 year old.

**Telzir** (fosamprenavir), another anti-HIV product, is now indicated in adolescents and children aged 6 years and above.

**Prevenar** (pneumococcal conjugate vaccine) is now indicated in the active immunisation of infants and young children from 2 months to 5 years of age against otitis media caused by *Streptococcus pneumoniae*, and against pneumonia (as opposed to bacteraemic pneumonia) caused by the same bacteria.

Positive opinions *not* resulting in a new indication (i.e. no extra indication in section 4.1 of the SPC)

In 2007, 3 applications were in this situation:
- One for **Acomplia** (rimonabant) received an opinion for the inclusion of results of submitted studies in section 5.1 of the SPC. These data were considered of clinical relevance to prescribers but not robust enough to support the proposed extension of indications to the treatment of Type II diabetes.
- One for **Avandia** (rosiglitazone) led to the removal of the contra-indication for the combined use of the product with insulins; although the aim of the application was to extend the indications to this combination.
- One for **Visudyne** (verteporfin) led to the deletion of one of the previously authorised indications (treatment of occult subfoveal choroidal neovascularisation due to age-related macular degeneration), although the aim of the application was to extend this particular indication.

- *Negative opinions and withdrawals*

The CHMP recommended 2 negative opinions in 2007.

**NutropinAQ** (somatropin), in the indication of long-term treatment of children with severe idiopathic short stature not explained by growth hormone deficiency or other medical conditions and with a predicted adult height at least 1 SDS below the target height.

**Zavesca** (miglustat), in the indication of treatment of neurological manifestations in patients with Niemann Pick type C disease.

However, both applications were subsequently withdrawn during their re-examination procedures.

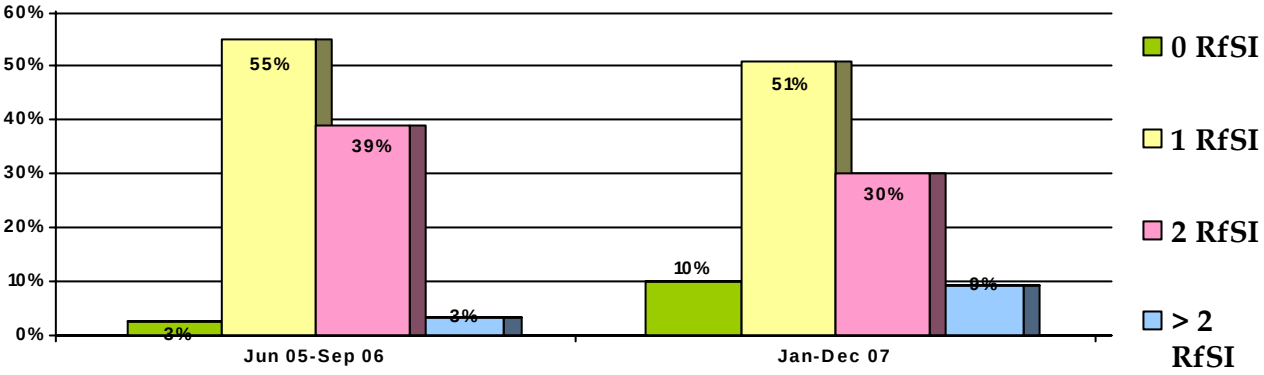
In addition, the MAH for **Zometa** (zoledronic acid) withdrew, prior to CHMP opinion, an application for an extension of indication for the prevention of fracture and bone loss in postmenopausal women with early-stage breast cancer treated with aromatase inhibitors.

Thorough 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

At least 1 RSI was adopted for most of the extension of indication procedures in 2007 (44/49). As shown in figure 13, a higher proportion of procedures were concluded without RSI (5/49) than in 2006. However, it is no longer exceptional to have more than 2 RSIs before opinion or withdrawal (4/49). Three of the 5 opinions adopted without RSI related to Glustin**,** which was a duplication of the assessment made for Actos in 2006.

**Figure 13:** Number of RSIs per procedure




In 2007, an increase in the proportion of procedures for which major objections were adopted (50% in 2007 vs. 36% in 2006) was observed. However, major objections do not seem to have a meaningful impact on the review times, including clock-stop times (figure 14 and table 6).

**Figure 14:** Kaplan Meier estimate of the survival function for the overall, active and clock-stop times

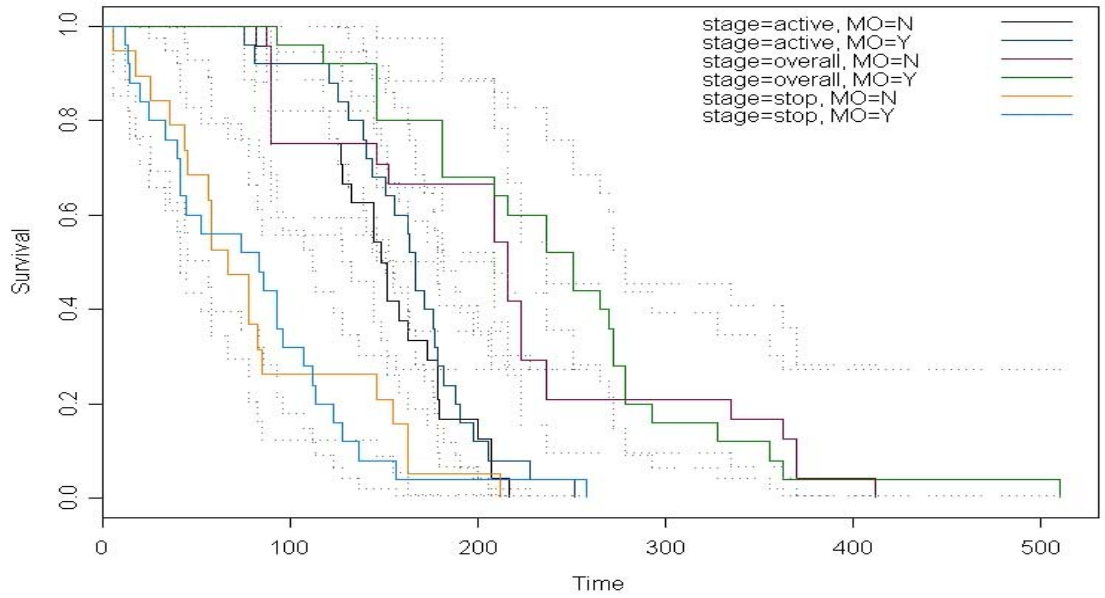



**Table 6:** Mean and median values of the overall processing time, active review time and clock-stop time, with and without major objections in 2007.

| | Major Objections N = 25 | | No Major Objections N = 24 | |
|---|---|---|---|---|
| | Mean (95% CI) | Median (95% CI) | Mean (95% CI) | Median (95% CI) |
| Overall time | 243 (209,277) | 251 (209,279) | 213 (174,252) | 216 (209,237) |
| Active time | 163 (148,178) | 167 (151,182) | 147 (131,163) | 152 (133,179) |
| Clock-stop time | 80 (58,102) | 84 (42,112) | 83 (58,108) | 67 (57,155) |

Eight applications included an oral explanation (16%). This is a two-fold increase compared to 2006 (8% of applications). In 4 instances, the oral explanation did not allow to solve major concerns raised by the

CHMP, as the applications resulted in 2 negative opinions, 1 withdrawal, and 1 deletion of indication. For the other 4 applications, the oral explanation contributed to reach a positive outcome.

More scientific advisory groups (SAGs) and ad-hoc expert meetings

The use of SAGs and ad-hoc expert meetings increased considerably in 2007, compared to 2006. Five SAGs and 1 ad-hoc expert meeting were called by the CHMP during the evaluation for 5 applications. No SAGs and only 1 ad-hoc expert meeting took place for extension of indication applications finalised between June 2005 and September 2006.

Three of the SAGs related to cardiovascular products (1 for **Arixtra** and 2 for **Angiox**). An anti-infectives SAG and a diabetes/endocrinology SAG took place to discuss issues arising during the assessment of **Cubicin** and **NutropinAQ** extensions of indications, respectively. The ad-hoc expert meeting related to **Remicade**, for the extension of the Crohn's disease indication to the paediatric population. SAGs and ad-hoc expert meetings may play an important role in the decision making process, by providing the CHMP with the position of experts on specific unresolved issues. In 2007, the CHMP outcomes were consistent with advice given by the SAGs and ad-hoc expert group prior to opinion.

Post-approval commitments

Seventy six percent of applications that were granted a positive opinion were adopted with post-authorisation commitments (75% in 2006). Commitments mostly related to efficacy and safety aspects. Of note, numerous pharmacovigilance related commitments were adopted. These typically include the update of the product risk management plan (RMP) in line with the new safety information assessed, the development and monitoring of risk minimisation measures in relation to new or already identified safety concerns, and the collection of long-term information on the safety of the products when used in the new populations (e.g. via registries, proactive observational studies, or long-term follow-up of ongoing studies).

This new trend for pharmacovigilance commitments may be partly explained by an increasing awareness and experience from industry and regulators on risk management and risk minimisation activities. Half (52%) of the opinions adopted for extension of indications presented updated RMPs. The EMEA peer-reviewed 85% of them during the assessments, thus contributing to the generation of related post-approval commitments. Updated RMPs were not necessary for the rest of the applications, for which the new indication was not considered likely to affect the already known safety profile of the product.

## 4. Scientific Advice (SA)

Scientific advice was given in relation to the sought new indication for 10 of the 49 procedures (20%), a figure comparable to 2006.

The small size of the sample studied 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 7), nor between prior SA and final outcome. However, such impact is complicated to assess, in particular for the following reasons:
- Relevant CHMP guidelines (or draft guidelines) were available for most of the new indications sought.
- Although SA is 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.
- An analysis on the level of adherence to the SA outcome is currently not available for extensions of indication, neither for MAHs or CHMP.

Of note, neither of the 2 negative opinions was subject to prior SA. The application withdrawn before opinion did receive prior SA in the indication sought. However, the issues raised by the CHMP during the evaluation in this case were consistent with the outcome of the SA.

**Table 7:** $\chi 2$ test assessing the impact of prior Scientific Advise on subsequent Major Objections

| | Major Objections | No Major Objections | Total |
|---|---|---|---|
| SA | 6 | 5 | 11 |
| No SA | 18 | 20 | 38 |
| Total | 24 | 25 | 49 |

Degrees of freedom: 1; $\alpha = 0.05$

Calculated $\chi^2$ value (0.176) < tabled $\chi^2$ value (3.84)