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

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REPORT ON WITHDRAWN CENTRALISED APPLICATIONS 1995-1998

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1. Introduction

The large increase in the number of withdrawn applications in the Centralised Procedure is a cause of concern among all parties involved. This was expressed at the EFPIA Infoday on 20 November 1998. These applications, if not withdrawn, would have led to a negative CPMP opinion.

A Working Group on Withdrawn Applications has been created at the EMEA within the Human Unit to analyse the withdrawals together with the CPMP. As a first result, this report is an analysis of regulatory and scientific aspects of withdrawn applications, such as the therapeutic areas, license status etc. It is also a first attempt to identify the specific CPMP concerns and objections associated with subsequently withdrawn applications.

Furthermore, a workshop on this topic involving CPMP and Industry was proposed at the EFPIA Infoday.

Together, these efforts aim to obtain useful advice for Applicants and information for the CPMP Members and the EMEA Secretariat.

The present report covers the withdrawals in the period from January 1995 to December 1998. During this period, a total of thirty centralised applications have been withdrawn. Of these, twelve are Part A and eighteen Part B products. Four of them are converted ex-concertation procedures and twenty-six are new centralised applications. From January 1995 to December 1998, a total of 103 full opinions (100 positive, 3 negative) were granted by the CPMP. These opinions relate to a total of 78 active substances.

The issues covered in this report are the following:

GENERAL ASPECTS ON THE WITHDRAWN PROCEDURES

- Trend in the number and type of withdrawn procedures along time (January1995-December1998)
- Type of product and therapeutic area (ATC code)
- Moment of withdrawal during procedure (list of questions, written response, oral explanation etc.)
- Duration of clock stops
- Intention to re-submit the withdrawn application

SCIENTIFIC ADVICE

- *Scientific advice* sought from the CPMP during the development process
- Time of scientific advice sought

MAIN CONCERNS RAISED BY THE CPMP

2. Results

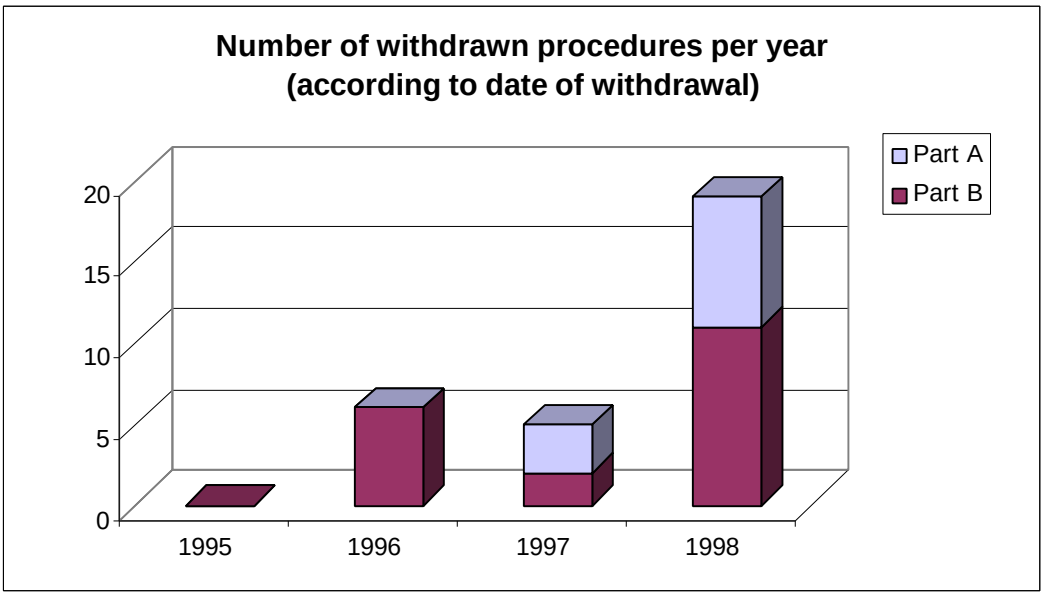
2.1 Number of applications withdrawn

So far, the withdrawal rate under the centralised procedure is 22.5% (30 withdrawals over 133 completed centralised procedures)[1]. The annual withdrawal rate is defined as the percentage of withdrawn applications compared to the number of completed procedures per year. The corresponding annual figures are given in Table 1.

	Annual withdrawal rate (withdrawals/ compl. procedures)
1995	0% (0/9)
1996	17.1% (6/35)
1997	16.1% (5/31)
1998	32.7% (19/58)

Table 1

The number of applications that are withdrawn is not distributed evenly over time, but there has been a substantial increase in 1998 (Graph 1).



Graph 1

[1] The withdrawal rate calculated on the number of active substances involved is 27.8% (30 withdrawn substances / 108 substances with completed evaluation).

Type of product and therapeutic area
The withdrawn procedures (Part A/B) according to the ATC classification:

- the largest class is products with an impact on *blood and blood forming organs [ATC Code B]* with nine procedures,
- six procedures fall into *antineoplastic and immunomodulating agents [ATC Code L],*
- four of the procedures are classified as *nervous system [ATC Code N],*
- three procedures fall into *systemic hormonal preparations [ATC Code H],*
  (for details see Table 2).

PART	THERAPEUTIC AREA/ATC code 1st level	ATC
B	Various	V
B	Blood and blood forming organs	B
A	Blood and blood forming organs	B
B	Dermatologicals	D
B	Cardiovascular system	C
B	General antiinfectives for systemic use	J
A	Systemic hormonal preparations, excl. sex hormones	H
A	Sensory organs	S
B	Systemic hormonal preparations, excl. sex hormones	H
A	Blood and blood forming organs	B
B	Blood and blood forming organs	B
A	Antineoplastic and immunomodulating agents	L
B	Nervous system	N
A	Nervous system	N
A	Antineoplastic and immunomodulating agents	L
B	Respiratory system	R
A	Blood and blood forming organs	B
B	Blood and blood forming organs	B
A	Blood and blood forming organs	B
B	Nervous system	N
B	Cardiovascular system	C
A	Various	V
B	Antineoplastic and immunomodulating agents	L
B	Antineoplastic and immunomodulating agents	L
A	Systemic hormonal preparations, excl. sex hormones	H
A	Antineoplastic and immunomodulating agents	L
B	Blood and blood forming organs	B
B	General antiinfectives for systemic use Antineoplastic and immunomodulating agents	J L
B	Blood and blood forming organs	B
B	Nervous system	N

Table 2

2.3 Main CPMP concerns

This evaluation represents the first attempt prepared by the EMEA Secretariat to better understand concerns raised by the CPMP preceding the applicant's decision to withdraw the application. The reasons specified are chosen according to the (Co-) Rapporteurs or CPMP-Assessment Reports as available at the time of withdrawal. The analysis is currently preliminary pending further discussion with the CPMP.

The methodological approach

Based on the currently withdrawn applications we categorised the main concerns as raised by the CPMP. This approach may harbour the risk of undue simplification but is the only way to make generalised recommendations based upon deficiencies in individual applications.

There are three main categories related to quality, efficacy and safety. In addition, a fourth category entails applications with major deficiencies in the documentation, categorised as Inadequate development/Premature data.

The main categories

- Quality: This category currently relates to methodological concerns.
- Efficacy: There are two main categories relating to "methodological concerns" and "magnitude of effect not acceptable", respectively. The main objective of the former categorisation is to highlight those main concerns, which prevent the CPMP from drawing conclusions on the clinically relevant effect. Such methodological concerns often lead to a request for new clinical trial data or new analysis of the available data.

  Concerns over the magnitude of effect may also be associated with methodological concerns, namely when the applicant tries to restrict the indication to a subgroup not originally described in the protocols or not covered by the application.
- Safety: There are two main categories relating to "Concerns over serious adverse events pertaining to products without conclusions on the clinically relevant effect" and "Overall safety profile not acceptable with respect to the observed clinical effect", respectively.

  For products in the former category it is not possible to enter into any benefit risk assessment since the relevant effect remains unknown (due to raised methodological concerns).

  For products in the latter safety category, safety concerns become more prominent and may render the benefit risk balance negative, particularly if the benefit of treatment is regarded as being marginal. However, a negative benefit risk balance could of course also apply to products with an outstanding clinical benefit although this does not seem to be the case for any of the currently withdrawn products.

The main concerns

- Efficacy: For most applications numerous concerns may be raised by the CPMP. All of these concerns may however not decisively influence the final decision on a recommendation for approval. For example, in most applications there are concerns over the justification for the dose or dose regimen. Although data to support an optimal dose recommendation is important and worthwhile, the ultimate CPMP decision will have to rely on the available efficacy and safety documentation with the proposed dose or dose regimen. Hence, concerns over dose have generally not been identified as a "Main Concern" (preventing conclusions on effect) in this classification.

  Thus, the main concerns, which are described under "methodological concerns", are the ones preventing the CPMP from concluding on the clinically relevant effect. They have been defined following analysis of the main deficiencies of the applications, individually and across products. This approach may contribute to a better understanding of how the CPMP reaches its conclusions.

For the concerns raised under "magnitude of effect..." the majority of cases relate to applications where marginal clinical efficacy is shown by the submitted data. In addition, the main concerns in this category entail applications with no relevant clinical evidence or inconsistent data on efficacy.

- Safety: There are four concerns which are identical under each main category (see below).

Results

(Individual withdrawn applications appear under different categories, which impacts on the calculations.)

Seven products (23%) were identified with inadequate development showing major deficiencies in different areas of the documentation.

There was only one product, which was withdrawn following main concerns over quality.

Twenty-one (70%) applications faced main concerns over efficacy (individual applications may contain several main concerns and appear under more than one category explaining the percentages given in the results).

Main safety concerns were raised against 15 (50%) applications.

The results are shown in Table 3.

Categorisation of Main Concerns raised by the CPMP for applications withdrawn from the centralised procedure (Table 3)

AREA	MAIN CATEGORY	MAIN CONCERNS	Preliminary Results*
	• **Inadequate development/ Premature data**	• Major Deficiencies in different areas of the documentation.	7 (23%)
Quality	• **Methodological concerns**	• Stability	1 (3%)
Efficacy	• **Methodological concerns (not allowing conclusion on the clinically relevant effect in the applied indication)**	• Concerns over study design (lack of controlled data) • Concerns over the hypothesis/analysis of pivotal data • Concerns over choice of endpoint • Concerns over choice of comparator • Concerns over selected population • Too few patients enrolled and/short duration of effect/or lack of long-term follow-up data • Concerns over the validity of the clinical trial data (e.g. major protocol violations)	14 (47%)
	• **Magnitude of effect not acceptable**	• Marginal clinical efficacy (including duration of effect) • No relevant clinical efficacy • Inconsistent data on efficacy	11 (37%)

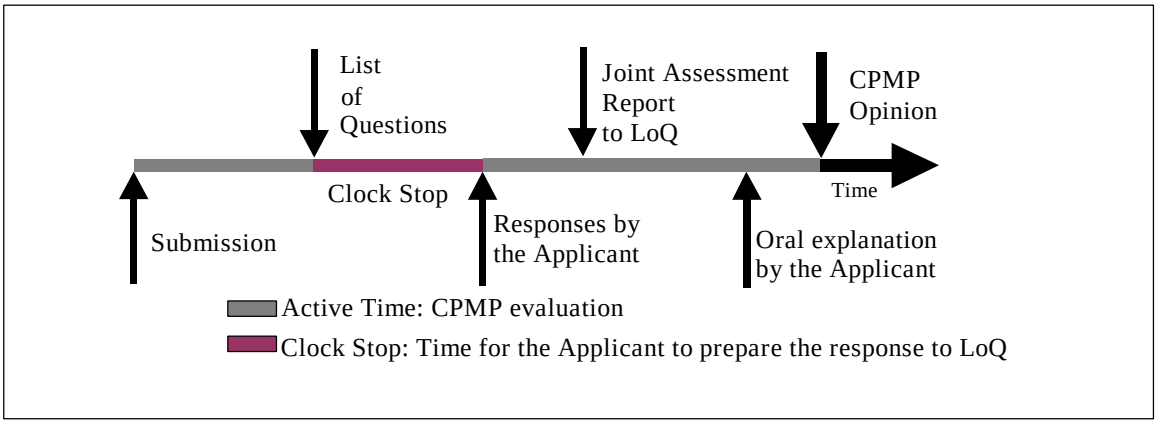
AREA	MAIN CATEGORY	MAIN CONCERNS	Preliminary results*
Safety	• **Concerns over serious adverse events pertaining to products without conclusions on the clinically relevant effect****	• Increased mortality • Other serious adverse events • Concerns over Size/Quality/long term data • Specific potential risks including preclinical concerns	5 (17%)
	• **Overall safety profile not acceptable with respect to the observed clinical effect*****	• Increased mortality • Other serious adverse events • Concerns over Size/Quality/long term data • Specific potential risks including preclinical concerns	10 (33%)

Table 3

* Individual applications may contain several main concerns and appear under more than one category explaining the percentages given in the results.
** This concern pertains to products appearing under Efficacy category, "Methodological concerns".
*** This concern pertains to products appearing under the category "Efficacy; Magnitude of effect not acceptable".

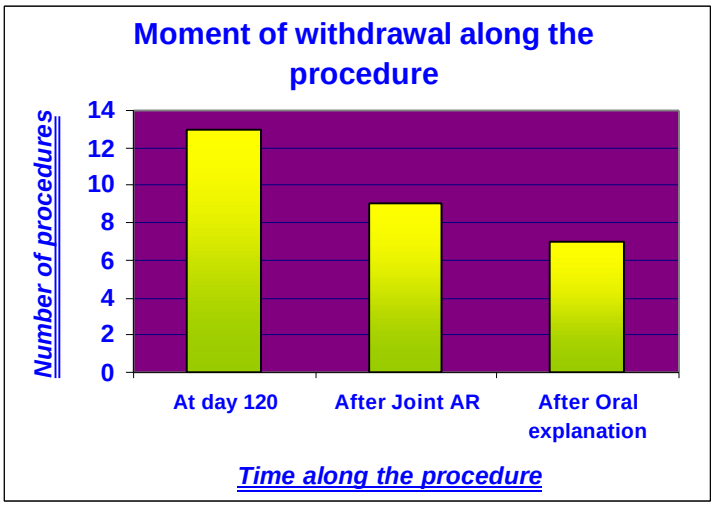
2.4 Moment of withdrawal in the procedure

Applicants may withdraw their application at different times in an ongoing procedure (Graph 2).



Graph 2

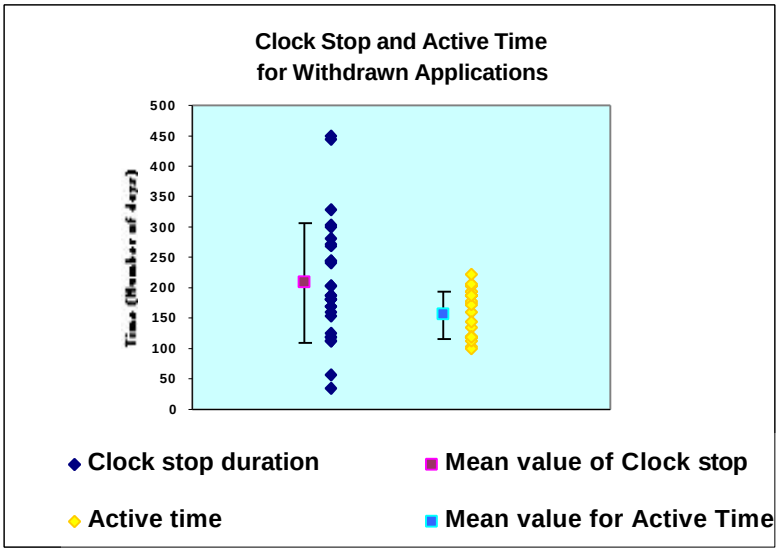
As can be seen in Graph 3, thirteen applicants withdrew their applications upon receipt of the *List of Questions* from the CPMP, and before the submission of the *Responses*, nine after considering the *Joint Assessment Report (AR) of the Responses to the List of Questions*, and seven companies withdrew after the *Oral Explanation, shortly before an opinion would have been issued by the CPMP.*



Graph 3

2.5 Duration of the clock stop for withdrawn procedures

Information on the duration of clock stop and active time values for withdrawn procedures is detailed in Graph 4.



Graph 4

The mean duration of the clock stop for withdrawn applications is 208 days while for the totality of the procedures the mean value is 157 days. The mean active time is however shorter in withdrawn procedures, 155 days, than in finalised procedures, 175 days – reflecting the large proportion of applications withdrawn at the List of Questions/Clock Stop time.

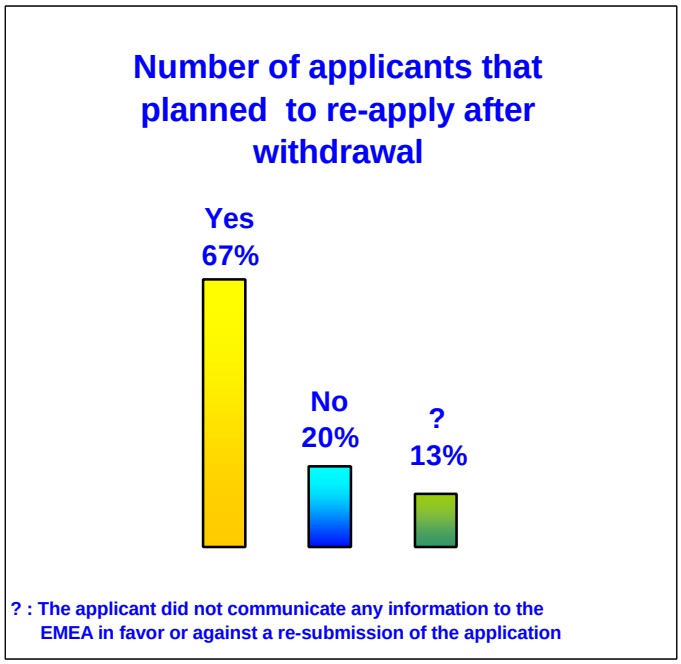
2.6 Scientific advice for withdrawn applications

As the period between receipt of scientific advice and submission of centralised applications is quite long (it is now increasing beyond four years) we expect that scientific advice will impact on the outcome of upcoming centralised procedures. Up until now only four applicants had sought for scientific advice from the CPMP prior to submission of a centralised application to be withdrawn later.

Out of these four, one applicant received a formal opinion on the question raised. Two other applicants preferred not to be given a formal advice letter. For the fourth product, the CPMP decided not to give advice on a future development programme for a new indication until the applicant would solve other major issues raised in the ongoing procedure. Moreover, one of the applicants sought advice when the review procedure had already started.

2.7 Intention to re-submit the withdrawn applications

The intention of the applicants to re-apply after withdrawal of a centralised application is detailed in Graph 5.



Graph 5

Two thirds of the applicants involved in a withdrawn procedure communicated their plan of re-submission to the EMEA. Only 20% did not consider re-submission and 13% did not disclose their intentions. Up until April 1999 the US FDA has authorised 8 (27%) of these products.

3. Conclusions

- The centralised procedure currently operates at an overall withdrawal rate of 22.5%.
- The withdrawal rate has increased considerably during 1998.
- The main concerns associated with withdrawal are efficacy concerns in 70%, safety concerns in 50%, and quality concerns in 3%. In addition, 7 (23%) applications were deemed to present inadequate development or premature data.
- Companies mainly withdrew their applications at day 120, i.e. after receiving the List of Questions from the CPMP. A smaller number withdrew the application after considering the Joint Assessment Report and an even smaller number after the Oral Explanation i.e. facing a negative opinion by the CPMP.
- The average clock stop for withdrawn procedures is approximately two months longer than the average for the totality of procedures.
- There are currently insufficient data to assess the impact of scientific advice on the outcome of the procedure.
- Two thirds of the companies that withdrew their application announced their intention to re-apply and there are products currently undergoing a new CPMP assessment.

Up until April 1999, the US FDA has authorised 8 (27%) of these products.

Any comment should be sent to Dr Bo Aronsson at the EMEA.