

ANALYSIS OF WITHDRAWALS IN THE MUTUAL RECOGNITION PROCEDURE

In order to identify the real causes of partial withdrawals and to suggest solutions for the future, the MRFG undertook an in-depth analysis of the reasons for withdrawals.

1 – Overview of partial withdrawals in the Mutual Recognition Procedure :

During the three years of the transition period (1995-1997), 249 new applications have been finalised through the mutual recognition procedure. 112 (**46%**) of them were finalised with at least one CMS withdrawn. With regard to the corresponding 2046 national final decisions issued by the CMSs, 247 national applications (12%) were withdrawn.

During the following years (1998-2000), 616 new applications have been finalised through the mutual recognition procedure. 223 (**36%**) of them were finalised with at least one CMS withdrawn.

The table below describes the situation and confirms that even if there is a slight decrease in the percentage of withdrawals, it remains an issue that needs to be considered.

	1995-1997	1998	1999	2000 (30/09)	TOTAL
Nb procedures finalised	249	180	253	183	865
Nb and (%) of procedures with at least one CMS withdrawn	112 (46%)	85 (47%)	71 (28%)	67 (36%)	335 (39%)
% of withdrawn national applications related to all CMSs	12%	16.5%	8.2%	5.5%	10.5%

2 – In-depth analysis of a sample of MR procedures with partial withdrawal(s):

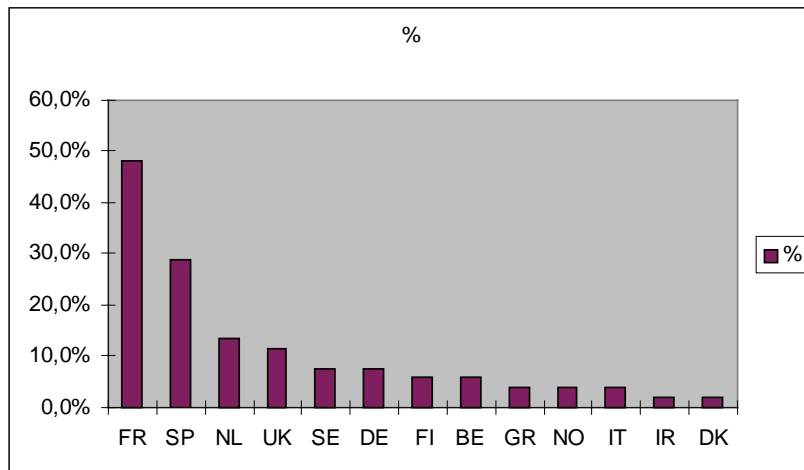
An in-depth analysis has been conducted by the MRFG from 1999 and restricted to those procedures in which one or more of the concerned member state(s) was/were withdrawn. A withdrawal report has been prepared by each RMS describing the procedure, highlighting any important factor or giving some recommendations on how to solve or avoid this kind of problems in the future.

The following results represent a specific analysis of the procedures finalised between 1st April 2000 and 30th September 2000.

Among 142 procedures finalised during this period of time, there were 52 (36%) procedures for which at least one CMS was withdrawn before day 90.

2.1 - Distribution per country

The graph below describes the distribution of CMS (expressed as percentage of withdrawals for each country among the total of withdrawals) in the above mentioned sample of procedures.



3.2 - Distribution per type of application

The distribution of the different types of applications as mentioned in the withdrawal reports is described in the following table.

- 48,7% of applications are involving **generic** products;
- 31% correspond to **new applications** (new chemical entity, new pharmaceutical form, new dosage, new route of administration or new indication).
- The **“Others”** category (20,5%) include different kinds of medicinal products such as well-known active substance submitted as bibliographical applications or new combination of well-known active substances.

NEW APPLICATIONS	31 %
<i>New chemical entity</i>	10,3 %
<i>New pharmaceutical form</i>	7,7 %
<i>New dosage</i>	5,1 %
<i>New route of administration</i>	5,1 %
<i>New indication</i>	2,6 %
GENERICS	48,7 %
OTHERS	20,5 %

3.3 - Distribution per reasons for withdrawals

The unsolved major objections leading to withdrawal were mostly related either to the assessment of the dossier or to SmPCs issues. The detailed distribution of reasons of withdrawals is given in the following table.

DOSSIER	38 %
<i>Safety/Efficacy</i>	23 %
<i>Quality</i>	10 %
<i>Bioequivalence</i>	5 %
SmPC	57%
Miscellaneous	5 %

A) SmPCs major objections leading to withdrawals were observed in 57% of applications.

- Generic products are mainly concerned when there is a disharmony of the information of the originator in the CMS withdrawn and the information of the final agreed SmPC.
- The main concerned sections are the « indications », « contra-indications », « special warning and precautions » sections but also the « pregnancy » section.
- Sometimes, the disharmony with the originators' indications and contraindications reflects local practices and nomenclature of diseases at the time where the medicinal product was licensed.
- One can mention that withdrawals have occurred even when there is an European « Class-labelling ». This may highlight that some difficulties are faced for the update of these « class-labelling » or for their national implementation...
- It should be highlighted that for 18% of withdrawals, problems of bioequivalence were also combined with SmPCs issues (see paragraph B).
- As far as repeat-use MRP is concerned, it has been reported that it is difficult to perform subsequent procedures as long as the SmPC agreed in the first round MRP cannot be changed during forthcoming ones.

B) Problems related to the assessment of the dossier were raised in 38% of cases :

• First of all, it should be highlighted that two kinds of concerns have been reported in this survey :

- dossiers for which a first negative opinion was given for scientific reasons
- dossiers considered as insufficient because of missing data

• Nevertheless, the distribution is the following :

- *Bioequivalence issue as only* (5%) : The main problems linked to the interpretation of bioequivalence were the following :
 - choice of the reference product
 - size of the batch used for the bioequivalence study
 - interpretation of C_{max}
 - sustained release forms (need for a steady state study, influence of food).
 These problems may be solved with the finalisation of the Note for Guidance on the investigation of bioavailability and bioequivalence.
 Moreover, as mentioned above, it should be noted that some bioequivalence issues were raised in combination with SmPC issues.
- *Quality issues* (10%), such as specifications issues or old DMF not updated in accordance with current guidelines...
- *Safety/Efficacy issues* (23%) are linked to differences in the assessment of the benefit/risk ratio. Moreover, it may occur that difficulties are encountered when an active substance is considered as a new chemical substance in several concerned member states, whereas it has been approved for many years in others or when applications are submitted just when a Note for Guidance has been recently approved : the dossier is therefore not in full accordance with this recently finalised guideline.

C) « Miscellaneous » (5%)

Several causes are included in this category such as the difference in the classification of the product in the member states, the absence of an adequate comparator in the national market...

Conclusion

This analysis brings forth reasons of withdrawals in mutual recognition procedure, which suggest or confirm strategies to prevent such withdrawals in the future. The MRFG has recently made some concrete proposals about the improvement of the mutual recognition procedure which may help in the future, such as the need to extend the period for scientific discussions or to improve the break-out sessions.