European Medicines Agency
Inspections

London, 21 July 2008
Doc. Ref. EMEA/INS/S&T/386434/2008

1998-2007

TEN YEARS OF SAMPLING AND TESTING OF CENTRALLY AUTHORISED PRODUCTS

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 95
E-mail: mail@emea.europa.eu http://www.emea.europa.eu
©EMEA 2008 Reproduction and/or distribution of this document is authorised for non commercial purposes only provided the EMEA is acknowledged

Index

©EMEA 2008

1. Introduction

When it was established in 1995 by the EC Regulation 2309/93, one of the tasks given to the newly formed European Medicines Evaluation Agency (EMEA) was the co-ordination of the supervision, under practical conditions of use, of medicinal products authorised within the community. In order to comply with the above obligation, the EMEA prepared (in consultation with its Scientific Committees and Working Parties, the European Commission, the EDQM and the Official Medicines Control Laboratories) a proposal for the implementation of Programmes of sampling and testing of Centrally Authorised Products. These programmes were to be co-ordinated by the Inspections Sector of the Agency, and the practical execution was to be carried out with the co-operation of the European Directorate for the Quality of Medicines - EDQM[1], the national competent authorities (for the sampling activities) and the Official Medicines Control Laboratories (for the products testing).

The regulation referred to above was superseded by Regulation (EC) 726/2004 which introduced several changes to the role of the Agency (including a change of name to European Medicines Agency). One of the changes defined more clearly the role of the EMEA and of the national authorities in the context of sampling and testing.[2]

The first programme of sampling and testing was carried out between 1998 and 1999 (with the preparatory work which initiated already in 1997), and in those years the products tested were limited in number. The aim of the first programme (trial programme) was to establish the basic procedures for the implementation of the programmes that were to follow. Starting with the years 1999-2000, full-scale programmes were established and implemented. At present about 40 products are tested each year, with the involvement of the NCAs (National Competent Authorities) and laboratories of the countries of the European Economic Area[3].

The aim of this document is to provide information and results in relation to the first ten years (1998 – 2007) of implementation of the above mentioned monitoring activity. Additionally it will also try to give an indication on the main developments expected for the programmes in the years to come.

[1] Now European Directorate for the Quality of Medicines and Healthcare - EDQM

[2] Art. 57 (r) of Council Regulation (EC) 726/2004 requires the EMEA to co-ordinate the supervision of the quality of medicinal products placed on the market, by requesting testing of compliance with their authorised specifications by an Official Medicines Control Laboratory or by a laboratory that a Member State has designated for that purpose

[3] The European Economic Area (EEA) includes the EU Member States and Iceland, Norway and Lichtestein

©EMEA 2008

2. The products tested

2.1 The selection of products

The trial programme carried out in 1998 comprised only 9 products; these were selected according to a range of criteria which included, among the others, therapeutic categories, market availability, stability and manufacturing process.

On the basis of the experience gained during the trial programme, in 1999 the EMEA Scientific Committees endorsed a document outlining the arrangements for the implementation of the sampling and testing programmes. Criteria for selection and inclusion of the products in each annual programme were agreed, the main criterion being the date of granting of the marketing authorisation. It was decided that the medicinal products would be included in a programme three years after the original centralised marketing authorisation had been granted.

The above 'three years' rule served different purposes. Firstly, since it is not unusual that products authorised are not immediately manufactured and marketed, it allowed for the inclusion in the programmes of those products whose marketing was delayed. Secondly, it gave companies some time to adjust their manufacturing and control processes, on the basis of the experience gained from full scale production. Finally, it provided the possibility to look at product quality at various stages of its shelf life.

On the basis of this approach every year the Inspections Sector prepared a list of products to be tested, that was submitted for endorsement by the EMEA Scientific Committees (CVMP and CHMP).

For the first years (until 2003) focus was on those products to be tested for the first time. However it became clear that a mechanism was needed to allow for the re-testing of previously tested products. This became even more evident during the 2004 Programme when, for the first time, on suggestion of the scientific committees, a medicinal product for human use was selected for retesting in an annual programme. A second product was re-tested in 2005, and since then this number has increased steadily.

Table 1: Number of products tested each year – products tested for the first time and products re-tested

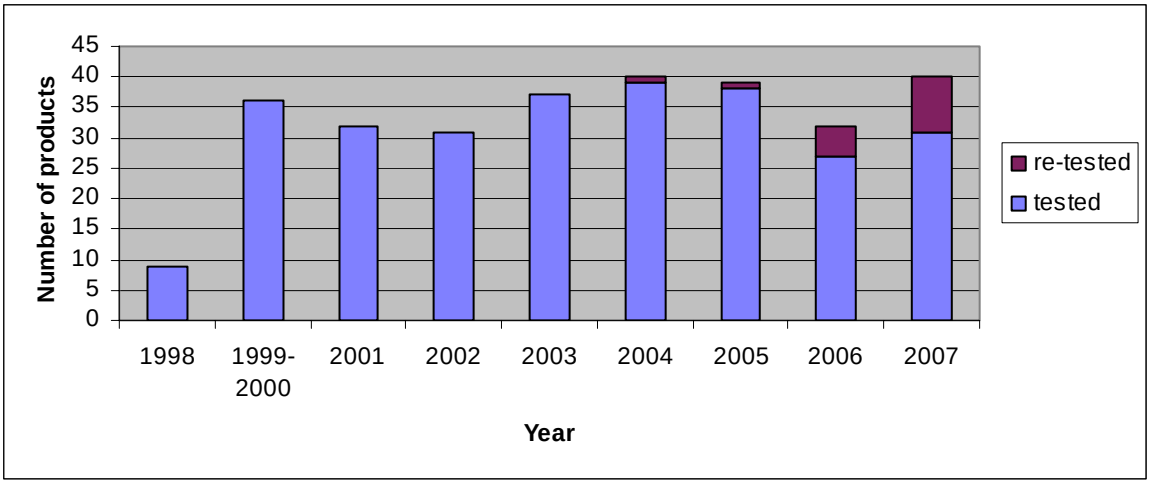
Year	Tested	Re-tested	Total
1998[4]	9	0	9
1999-2000[5]	36	0	36
2001	32	0	32
2002	31	0	31
2003	37	0	37
2004	39	1	40
2005	38	1	39
2006	27	5	32
2007	31	9	40
Total 1998-2007	**280**	**16**	**296**

[4] Trial programme: a limited number of products was tested

[5] Following the trial programme, the programmes for the years 1999 and 2000 were grouped together

©EMEA 2008

Graphic 1: Number of products tested each year – products tested for the first time and products re-tested



Another important aspect to be considered, in relation to the selection of the products, was the need to strike a balance between the growing number of products authorised, and the resources allocated to the project, which had remained more or less constant since the beginning.

One of the solutions proposed to address this problem was to abandon the "three-years" criterion used for the selection of products, in favour of a selection which makes use of a "risk-based" approach. The EMEA recognised the validity of such an approach and started to work on this topic.

According to a proposal currently under development, all products authorised would be assessed against defined risk factors. These risk factors would consider both the probability of achieving an adverse outcome in the testing (in our case, problems with the performance of the testing and/or with the testing results), and the possible consequences of this outcome. The products would be then ranked against these factors, and the list of products to be tested every year would take account of this ranking.

2.2 Human vs. veterinary, chemical vs. biological

The Agency has responsibility for the evaluation of medicinal products for human use and for the evaluation of veterinary medicinal products; for this reason, since the beginning, both human and veterinary products were included in the sampling and testing exercise.

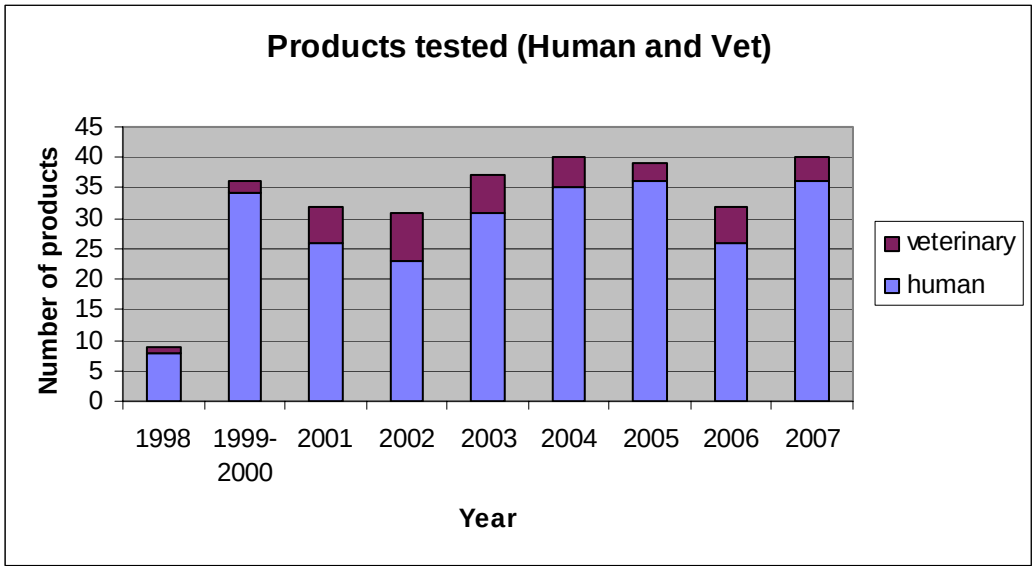
There is, however, a significant difference in the number of applications (and in the number of opinions issued and authorisation granted) for human and veterinary medicinal products that the Agency receives every year. This is reflected in the number of products that were tested in each annual programme (see table 2).

©EMEA 2008

Table 2: number of products tested each year – medicinal products for human use and veterinary medicinal products

Year	Human use	Veterinary use	Total
1998	8	1	9
1999-2000	34	2	36
2001	26	6	32
2002	23	8	31
2003	31	6	37
2004	35	5	40
2005	36	3	39
2006	26	6	32
2007	36	4	40
Total 1998-2007	**255**	**41**	**296**

Graphic 2: number of products tested each year – medicinal products for human use and veterinary medicinal products



Similar considerations can be done in relation to the testing of chemical and biological products. Also in this case, as it is normal to expect, this distribution reflects the pattern of the authorisations granted (table 3).

Table 3: biological/veterinary immunological products vs. chemical products

- Year	Human (Total)	Human Biological	Human Chemical	Veterinary (Total)	Vet. Immun.	Vet. Chemical	Total
1998	8	4	4	1	1	0	9
1999-2000	34	12	22	2	1	1	36
2001	26	3	23	6	2	4	32
2002	23	8	15	8	1	7	31
2003	31	12	19	6	2	4	37
2004	35	10	25	5	2	3	40
2005	36	11	25	3	2	1	39
2006	26	6	20	6	2	4	32
2007	36	12	24	4	2	2	40
Total 1998-2007	**255**	**78**	**177**	**41**	**15**	**26**	**296**

©EMEA 2008

It should be noted that those biological products for human use subject to Official Control Authority Batch Release are not included in the above statistics. These products are systematically tested in one of the European OMCLs before they are released on the market, and are therefore excluded from the sampling and testing programmes.

Additionally, since 2007 an Official Control Authority Batch Release (OCABR) [6] pilot scheme has been also put in place for immunological veterinary products. The EMEA will take into consideration the implementation of this new scheme when deciding on the inclusion of veterinary immunological products in future testing programmes.

2.3 Pharmaceutical Forms

The indication of the pharmaceutical forms tested (Table 4) reflects the types of dosage forms that have been authorised over the years.

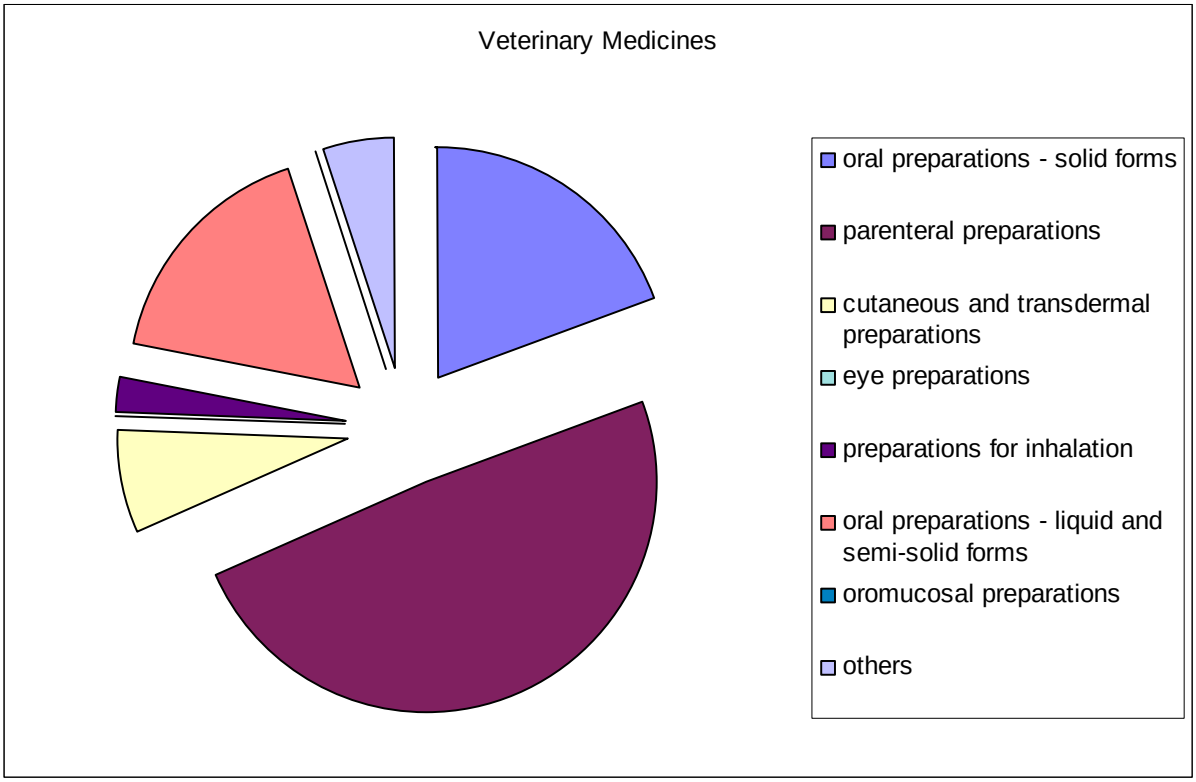
Table 4: distribution of products tested according to the pharmaceutical forms

Pharmaceutical form	Human	Veterinary	Total
Parenteral preparations	114	20	134
Oral preparations – solid forms	95	8	103
Oral preparations - liquid and semi-solid forms	25	7	32
Cutaneous and transdermal preparations	7	3	10
Eye preparations	5	0	5
Preparations for inhalation	2	1	3
Oromucosal preparations	2	0	2
Others	5	2	7
Total	**255**	**41**	**296**

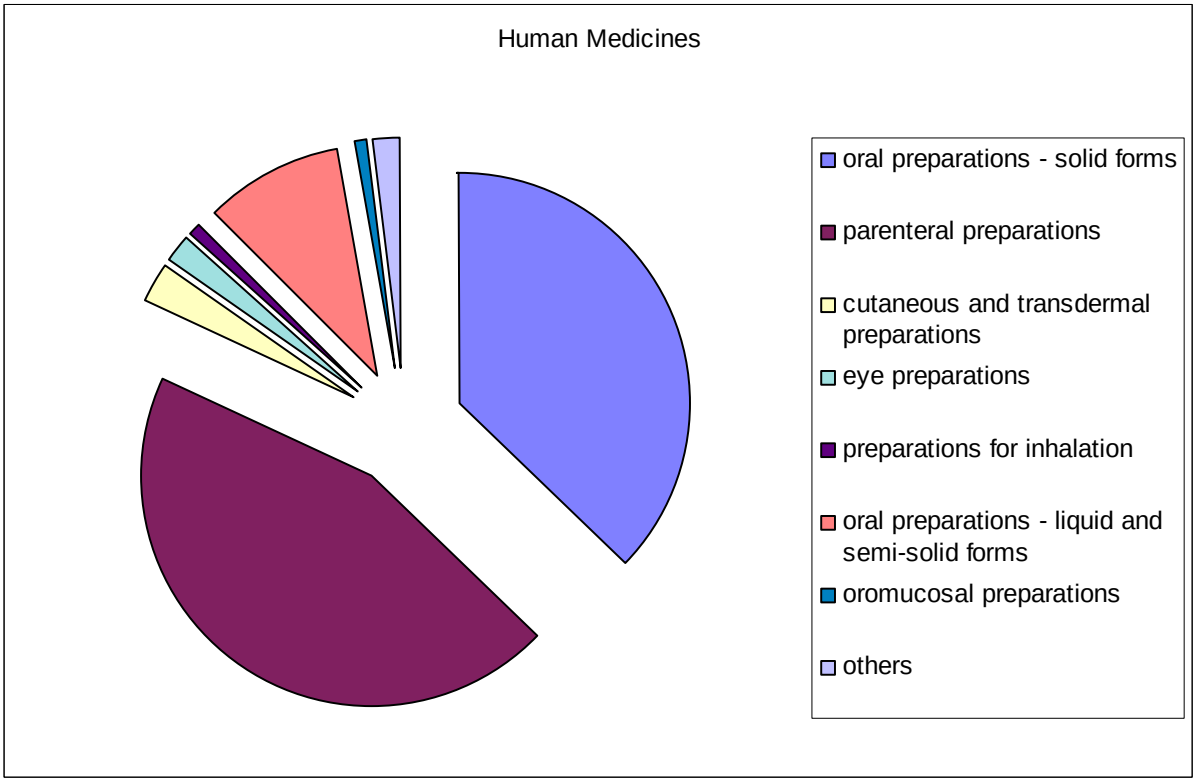
[6] Art. 82 of Directive 2001/82/EC as amended by Directive 2004/28/EC

©EMEA 2008

Graphic 3: Breakdown of Veterinary medicinal products according to the pharmaceutical forms



Graphic 4: Breakdown of medicinal products for human use according to the pharmaceutical forms



©EMEA 2008

3. The selection of the testing parameters

The contribution that the members of the EMEA Scientific Committees have given to the positive outcome of the monitoring programmes so far, has been extremely important. It is the responsibility of the Scientific Committees to endorse the list of products to be tested each year. But their role is not limited to this task. They have also been actively involved in the identification of the parameters to be tested and, as we shall see later on, in the follow-up actions.

The procedures currently implemented establish that during the preparatory stage, once the medicines to be tested have been identified, the Rapporteur and CoRapporteur for each product are consulted in relation to the critical quality parameters to be analysed. The in-depth knowledge of the product, for which the Rapporteurs and their teams are responsible, makes them the most suited to perform this task.

The advice provided by the Rapporteurs represents an important piece of information, which can have a crucial impact on the subsequent steps of the Programme. The types of parameters selected can, for example, affect the quantity of product to be sampled, the complexity of the testing and, as a consequence, the choice of the laboratories involved.

It has become clear that also this part of the procedure could be improved and streamlined. Inspections Sector has already started to look into the possibility to request and gather the testing recommendations in advance, possibly at the stage in which the product is evaluated and the first assessment report is prepared by the Rapporteurs. Work in this direction is already well-advanced. At present a template for the testing recommendation is included in the day 80 Assessment Report (Quality) to be completed by the Rapporteur and CoRapporteur for the Human medicinal products. A similar template is circulated, for completion by the Rapporteur and CoRapporteur of veterinary products, at day 121 of the assessment procedure.

Additional work is currently being carried out for the purpose of achieving harmonization, in terms of testing parameters, for products which are similar. On the basis of the experience reported by the national authorities, it has been seen that similar products are tested for a well defined and restricted range of parameters. This is not always the case for the Centrally Authorised Products. Guidance on this topic is in preparation at present, and will be subject to further discussion and study.

The choice on the critical quality parameters operated by the Rapporteurs, is reflected in the list of parameters which are tested in the finished product. In the first ten years of implementation of the Programme, the laboratories tested over 130 different parameters. Table 5 shows a list of the parameters that have been tested more often.

Table 5: parameters tested in the drug products

Appearance	Identity	Assay	Protein content	Preservative content
Dissolution	Purity	Activity	Solubility	pH
Uniformity of content	Uniformity of mass	Moisture content	Water content	Molecular weight
Sterility	Endotoxins	Chemical impurities	Biological impurities	Colour
Clarity	Reconstitution time	Potency	Density	Loss on drying
Disintegration	Osmolality	Particle/bubble/droplet size	Volume	Average mass

In addition, it is not unusual that the Rapporteurs also recommend the testing of the active substance. In the first ten years, this has happened in 45 cases, and the laboratories tested over 40 different parameters. Table 6 shows a list of the parameters that have been tested more often.

©EMEA 2008

Table 6: parameters tested in the drug substance

Appearance	Identity	Assay	Protein content	Water content
Activity	Purity	Chemical impurities	Potency	Peptide mapping
pH	Particle size	Endotoxins	Loss on drying	Optical rotation

4. The involvement of the MAH

Once the products have been identified - and at the same time in which the request for testing recommendations is sent to the Rapporteurs - the Marketing Authorisation Holders (of the products selected) are also informed of the inclusion of their products in the annual programme.

They are requested to provide the information and documentation necessary for the organisation and implementation of the programme. The MAHs are expected to provide a wide range of information and documents, including the relevant information on the quality of the product which, at least for human products, is contained in Module 2 and Module 3 of the CTD – Common Technical Document; information on the staff to be contacted prior to or during the testing; information on the marketing status of the product. Additionally the MAHs are also expected to provide material (one control sample and reference testing material) that is to be used for the practical testing by the OMCLs.

The quantity of documentation expected from the MAH has not changed significantly over the years. However, with the introduction of the CTD for the applications of human medicinal products, it is likely that it has become easier for companies to identify, retrieve and provide to the EMEA and EDQM the information requested.

5. The sampling phase

As mentioned above, companies are requested to provide information on the distribution of the product on the European Market. This information is used to plan the sampling phase. The actual sampling is then carried out locally, with the contribution of the National Competent Authorities, who provide samples of the products drawn from their respective markets.
In general each product is sampled in three different Member States, and the aim is to obtain samples taken from three different batches of the product. In the preparation of the sampling plan they are taken into consideration the climatic zones from which samples are drawn (North Europe, Central Europe and South Europe areas); the possibility of the inspectors to find and to sample the requested amount of pharmaceutical units; and the objective to achieve equal sharing of sampling among the inspectorates.

The involvement of the national competent authorities in the first years of implementation of the Programmes is detailed in Table 7.

Table 7: samples taken by national authorities

YEAR	**1998**	**1999/ 2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	
COUNTRY										**TOTAL (Country)**
Austria		6	5	4	7	5	4	3	5	39
Belgium	1	4	5	3	5	5	4	4	4	35
Cyprus								1	1	2
Czech Republic							4	4	2	10
Denmark	1	5	5	6	5	5	5	5	6	43
Estonia							2	1	3	6
Finland	1	6	5	5	3	4	6	4	5	39
France	3	9	6	9	10	11	8	8	7	71

©EMEA 2008

Germany	2	9	6	9	9	10	6	7	8	66
Greece	2	6	5	5	5	10	6	4	7	50
Hungary							3	2	5	10
Iceland (EEA)					1	1	1	2	2	7
Ireland	1	5	3	4	7	4	3	5	5	37
Italy	2	9	7	7	10	7	6	6	9	63
Latvia							1	1	1	3
Lithuania							2	1	2	5
Luxembourg	1	1	2	2	3	3		1	3	16
Malta								1	1	2
Netherlands	2	6	5	1	5	6	5	4	5	39
Norway (EEA)				2	1	3	3	1	4	14
Poland							1	2	4	7
Portugal	2	5	4	3	4	3	7	7	2	37
Slovakia							1	1	3	5
Slovenia							1	2	2	5
Spain	2	8	6	6	9	9	7	6	8	61
Sweden	2	5	4	5	6	5	3	3	8	41
United Kingdom	2	6	3	6	7	5	4	2	4	39
TOTAL (Year)	24	90	71	77	97	96	93	88	116	752

In view of the fact that one of the purposes of the sampling and testing programmes is to monitor the quality of the medicines available on the European market, the EMEA and the EDQM tried to engage as many different authorities as possible in the sampling phase.

In 2004, following the enlargement of the EU to 10 new Member States, the Sampling and Testing Programme was extended to the new countries. However, since the enlargement only occurred in May 2004, the active involvement in the sampling phase couldn't actually take place before the 2005 Programme.

The sampling phase, like others parts of the Programme, has undergone some changes during the first years of implementation. The most notable has been the introduction of a voucher replacement system in 2001. This system allows the staff of the national inspectorates to take samples e.g. in a community pharmacy, in exchange for a voucher for the product. This voucher can be later exchanged with replacement products from the MAH and corresponding to the amount sampled.

This system has made the sampling phase more efficient by avoiding problems linked to the necessity to purchase the samples needed for the testing.

6. The testing phase

The other major contribution given by the National Authorities to the implementation of the Sampling and Testing Programme, is through their involvement in the testing phase; their Official Medicines Control Laboratories (OMCLs) provide expertise and resources for the testing of the products sampled.

The work of the OMCLs is co-ordinated by the EDQM through its well-established OMCL Network, which includes those countries that are members of the European Pharmacopoeia. A restricted group of the Network (which includes only the laboratories of the EU/EEA countries) is involved in the testing of the Centrally Authorised Products.

The contribution of the national laboratories to the testing phase in the first years of implementation of the Programmes is detailed in Table 8.

©EMEA 2008

Table 8: testing operations on finished products carried out by national laboratories [7]

YEAR	1998	1999/ 2000	2001	2002	2003	2004	2005	2006	2007	
COUNTRY										**TOTAL (Country)**
Austria	1	4	3	1	3	4	3	1	3	23
Belgium		3	3	3	3	1	2	2	2	19
Cyprus						1	1	2	1	5
Czech Republic						1	1	3	2	7
Denmark	1	8	6	6	9	4	4	4	5	47
Estonia							4	1	1	6
Finland	1	5	5	4	6	5	4	2	3	35
France	6	10	8	8	11	12	8	5	6	74
Germany	4	11	9	8	7	11	13	8	5	76
Greece		4	4	2	1	2	2	1	1	17
Hungary						1	1	2	2	6
Ireland		1		3	2		1	4	1	12
Italy	1	2	3	2	2	2	5	2	1	20
Latvia								1	1	2
Lithuania							1	1	1	3
Luxembourg	1	1	1	1	1	2	1	1	2	11
Netherlands	3	3	6	3	2	4	3	3	2	29
Norway (EEA)		1	1	5	3	3	2	3	1	19
Poland						1	3	7	2	13
Portugal		3	4	4	7	9	4	6	4	41
Slovakia						1	1	1	1	4
Slovenia						1	2	1	1	5
Spain	1	2	2	1	2	3	1	1		13
Sweden	1	6	5	4	10	6	4	4	5	45
United Kingdom	4	8	4	8	6	6	5	5	3	49
Non EEA countries					2[8]					2
TOTAL (Year)	24	72	64	63	77	80	76	71	56	583

As already seen with the sampling, every effort has been made to make sure that as many laboratories as possible participated in the testing phase.

Norway, a member of the EEA, was involved with the testing right from the beginning of the regular Programmes (1999/2000).

Some of the countries that joined the European Union in May 2004 were involved in the testing phase as soon as they became Members of the Union: Cyprus, Czech Republic, Hungary, Slovenia and Slovakia tested 1 product each in 2004.

For the initial Programmes, testing was typically carried out in two different laboratories; this served the purpose of increasing mutual confidence in the results of the national laboratories, and as a way of cross verification of the results.

[7] In Malta, Liechtenstein (EEA) and Iceland (EEA) there are no national OMCLs
[8] Switzerland and Poland (in 2003 Poland was not yet a Member of the EU)

©EMEA 2008

However, based on experience gained in the previous years, in the year 2005 a simplified testing scheme (consisting in the use of a single laboratory) was implemented for the testing of chemical products. This new approach was phased out over a three year period, and by 2007 all chemical products were tested using a single laboratory only.

The new testing scheme allowed the national laboratories to reduce the resources allocated to the CAP Testing Programme. Additionally, the reduced number of testing laboratories meant that a reduced quantity of product was sampled from the market.

The EMEA, in co-operation with the EDQM and the OMCLs network, is currently evaluating the possibility to implement single laboratory testing for biological products. Due to the specific characteristics of these medicines, such an approach might be problematic, and any further development in this direction will be carefully evaluated.

7. Bringing the annual programme to a conclusion: testing results and follow-up actions

After the products were tested by the OMCLs, the raw data and the comments of the testing laboratories on the results and on the testing methods were sent to the EDQM. The EDQM used this information for the preparation of individual testing reports (one for each product).

The individual testing reports were provided, on an on-going basis, to the EMEA which had the responsibility for the follow-up actions. These reports contained, in addition to the results obtained by the testing laboratories, comments and recommendations on possible actions.

During the first three years of implementation of the programme (1998 and 1999/2000), out of 45 products tested, about half of them (22) didn't raise any problem; for the remaining 23 some issues where identified.

It was only at a later stage that, on the basis of a proposal of the EMEA and in order to better clarify the final outcome of the testing, it was agreed to classify the testing results according to the following 4 groups:

1. All results comply – no problems identified
2. Issues identified to be taken up with experts/rapporteur/co-rapporteur
3. Out of specification results
4. Health risk

Table 9 shows the results of the testing carried out, classified according to the above scheme

Table 9: testing results

Year	Number of products tested	Testing result: no problems identified	Testing results: issues of technical, regulatory, scientific, editorial nature identified	Testing results: out of specification results	Testing results: health risk
2001	32	16	12	4	0
2002	31	13	17	1	0
2003	37	11	25	1	0
2004	40	14	22	4	0
2005	39	23	16	0	0
2006	32	9	21	2	0
2007	40[9]	22	16	1	0

[9] One of the products included in the 2007 Programme was tested during the assessment stage (before its authorisation and marketing). Testing was requested to verify the suitability of the testing methods. Nothing can therefore be said in terms of compliance with its authorised specifications.

©EMEA 2008

The table shows that every year there was a number of products, either with some issue identified or with out of specification results, for which the EMEA was expected to take action in order to follow-up to the testing results. The experience gained as the programmes progressed, allowed the EMEA to develop specific procedures for the implementation of consistent and rapid actions.

In addition the circulation of the reports (to the MAHs and to the Rapporteurs) was streamlined, and it was made faster and safer with the use of Eudralink, an email system specifically designed for the circulation of confidential documents.

The Rapporteurs play an important part in the follow-up, since any action taken is based on their competent advice. This can include e.g. re-testing of the product, seeking clarification with the MAHs in relation to specific issues, investigate issues during ad-hoc or routine inspections.

Most of the problems identified during the testing were dealt with through communication and clarification involving (depending on the issue) the MAHs, the EMEA Secretariat, the Rapporteurs, the EDQM and the testing laboratories. This resulted, in some cases, in the MAH amending the testing methods or the relevant SOPs (when needed, through variations).

In other cases, especially when problems of compliance with the quality specifications had been identified, other regulatory actions (Quality Defect procedure, re-testing, inspections) were deemed to be necessary.

However, no quality issues identified were serious enough to be classified as immediate health risk.

8. Looking at the future

In the short to medium term we do not foresee major changes to the sampling and testing programme. EMEA has recently outlined a strategy for introducing a risk-based approach[10] to the selection of products for inclusion in each annual programme rather than automatic inclusion on the 3rd anniversary of authorisation. This will be partially implemented in the 2009 programme for human medicinal products. The aim is to optimise the use of Member States' official laboratory resources in the annual programmes.

Another change under active consideration is the inclusion of samples that have undergone parallel distribution. Checks on the packaging and labelling of these products will be carried out in addition to analytical testing of the products.

9. Conclusions

Starting in 1998 with a trial phase involving only nine Centrally Authorised Products, the Sampling and Testing Programme, organised and coordinated annually by the EMEA in co-operation with the EDQM, has developed into one of the key tools for monitoring the quality of the centralised products available on the European Market.

Between the years 1998 and 2007, a total of 280 products were tested, which represented a significant proportion of the products authorised through the centralised procedure.

The Sampling and Testing Programme complements similar surveillance programmes, which are carried out at national level and which mainly focus on nationally authorised products and/or those authorised through the mutual recognition procedure.

The programme relies on the cooperation, resources and competences provided by the national authorities, and therefore helps to foster collaboration and mutual confidence among the EEA Member States.

[10] Sampling and Testing of Centrally Authorised Products: Development of risk based approach for the selection of products. EMEA/INS/S&T/120857/2008, 10 January 2008.

©EMEA 2008

The suggestions and the advice provided to the EMEA, coming from the national authorities that operate similar projects, have certainly helped to develop and improve the Programme during the years.

Further improvements are currently under consideration, which should allow for a better use of the resources made available to the EMEA for this activity.

Acknowledgement
Thank you to Ms. Özlem Daylan (Turkish Visiting Expert) for her contribution to the collection and elaboration of data.

©EMEA 2008