20 years of Sampling and Testing of Centrally Authorised Products

1998 – 2017

Index

1. Introduction

The European Medicines Agency (EMA) together with the European Directorate for the Quality of Medicines & HealthCare (EDQM) and the Official Medicines Control Laboratories (OMCL) Network organise a yearly sampling and testing programme to verify centrally authorised medicinal products (CAPs) place on the EU market.

The purpose of the CAP programme is to supervise the quality of centrally authorised medicinal products that are placed on the EU/EEA market, in all parts of the distribution chain, by testing their compliance with their authorised specifications. In addition, testing OMCLs check that the authorised control methods are suitable for their intended use.

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

The programme was started in 1997-1998 with a trial phase which included a limited number of products. Following the successful completion of the trial, routine annual programmes were implemented beginning with the years 1999/2000. Between 1998 and 2017, more than 700 products were tested, representing a significant percentage of the total number of products authorised through the centralised procedure.

The EMA is the sponsor and has overall responsibility for the programme, whereas the EDQM co-ordinates the sampling and testing operations. The EDQM's duties include reporting the results of the testing programme and proposing follow-up actions, if necessary, to the EMA. National inspection services draw products from the market and members of the EU/EEA OMCL Network test these samples.

The sampling and testing phases of the programme are run by the EDQM on behalf of the EMA. This is possible thanks to the close collaboration between the EMA, the EDQM, the National Competent Authorities (NCAs) of the EU/EEA Inspectorates/nominated Sampling Contact Persons and the OMCL Network, and thanks to the co-operation of the Marketing Authorisation Holders (MAHs).

The aim of this document is to provide information and summarise the results of the above-mentioned monitoring exercise. Additionally, it gives an overview of the main developments, both ongoing and planned for the coming years.

2. Selection of products

1) How are the products selected?

The trial run organised in 1998 comprised 9 products that were selected according to a range of criteria which included, amongst others, therapeutic categories, market availability, stability and manufacturing process.

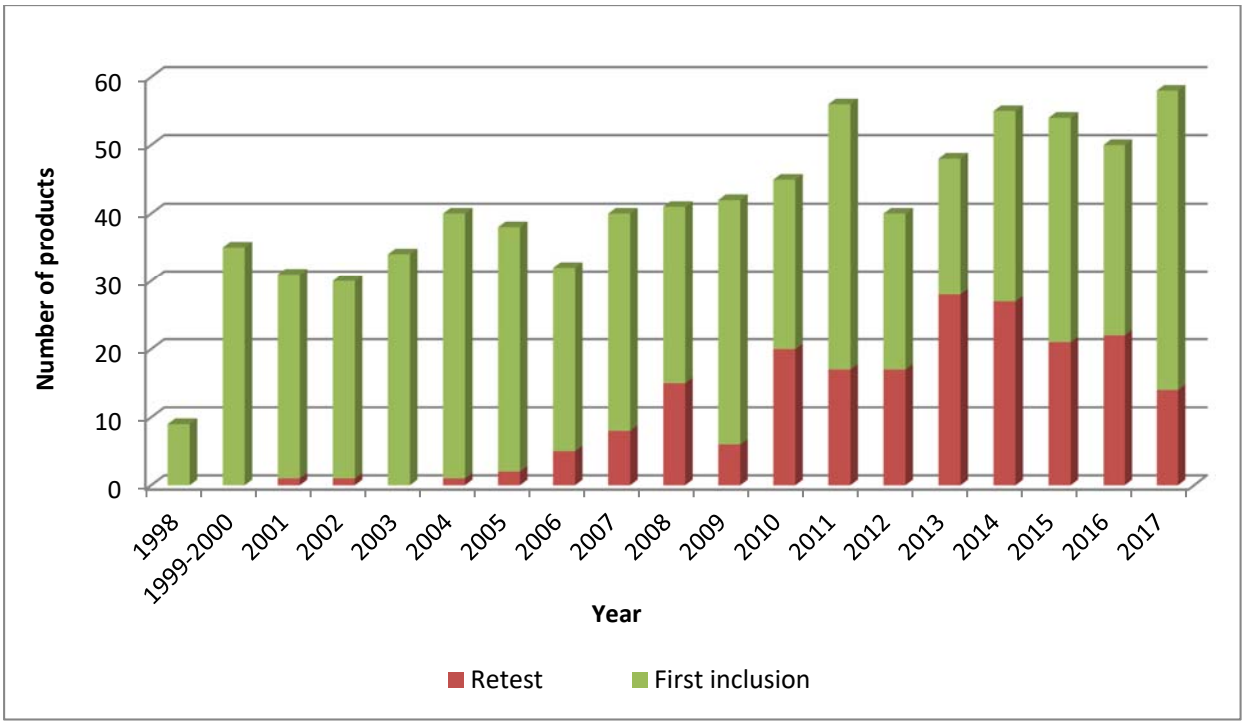
On the basis of the experience gained, criteria for the selection of products for each annual programme were agreed, the main criterion being the date of granting of the marketing authorisation. It was decided that CAPs would be included in the programme three years after the original centralised marketing authorisation had been granted.

During the early years, new products were selected for each programme. In 2004, at the suggestion of the scientific committees, one medicinal product for human use was selected for retesting; thus, it became evident that a mechanism allowing the retesting of CAPs which had already undergone the Sampling and Testing programme was needed. A second product was retested in 2005, and since then this number has increased steadily. Another important aspect to be considered in relation to the selection of products was the need to strike a balance between the increasing number of products authorised and the resources allocated to this project, which had remained more or less stable since the beginning. Consequently, the "three years rule" was abandoned in favour of selection using a "risk-based" approach.

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

Year	Retested product	First inclusion	Total
1998	0	9	9
1999-2000	0	35	35
2001	1	30	31
2002	1	29	30
2003	0	34	34
2004	1	39	40
2005	2	36	38
2006	5	27	32
2007	8	32	40
2008	15	26	41
2009	6	36	42
2010	20	25	45
2011	17	39	56
2012	17	23	40
2013	28	20	48
2014	27	28	55
2015	21	33	54
2016	22	28	50
2017	14	44	58

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



In 2007, the EMA started work on a risk assessment tool based on an OMCL Network model, considering findings from the assessment of applications for marketing authorisation and variations, GMP inspections and findings from previous testing of similar products or presentations. The selection criteria included risks identified for the active substance (e.g. narrow therapeutic range), intrinsic product characteristics such as poor stability or pharmaceutical form, complexity of the manufacturing process, patient profiles/exposure, etc.

Since 2009, the list of products to be tested has been prepared by the EMA using a risk-based approach; this list is then agreed between the EDQM, the EMA and the CAP Advisory Group members one year ahead of the testing phase. The proposed testing plan is normally approved at the February meetings of the Committee for Medicinal Products for Human Use (CHMP) and the Committee for Medicinal Products for Veterinary Use (CVMP). Typically, 40-45 products are tested per year.

It should be noted that biological products for human use (vaccines and human plasma-derived medicinal products), which are subject to Official Control Authority Batch Release (OCABR), are not included in the above statistics. These products are independently tested by an OMCL before they are released onto the market, and are therefore not considered for the sampling and testing programmes. Additionally, in 2007 an OCABR scheme was put in place for a number of Immunological Veterinary Medicinal Products (IVMPs); consequently, these products are also excluded from this programme.

2) Distribution between the different categories of products

Both human and veterinary products are included in the sampling and testing exercise as the EMA is responsible for the evaluation of human and veterinary medicinal products.

As the number of applications for human and veterinary medicinal products received every year is highly variable, the number of human and veterinary products tested in the CAP programme varies from year to year. The same principle applies to the testing of chemical and biological products where, as a rule, the ratio of products entering the testing programme reflects the number of authorisations granted.

Table 2: Distribution of the categories of products tested every year

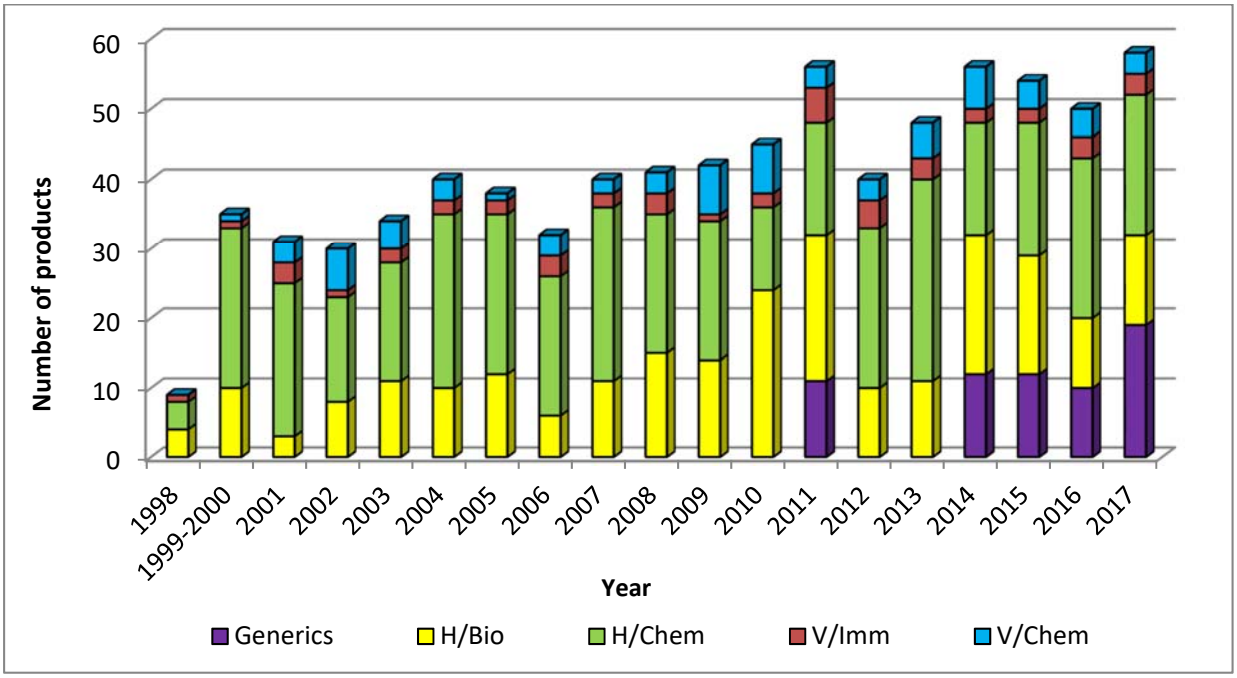
Year	Generics	H[1]/Biological	H/Chemical	Vet[2]/Imm.[3]	Vet/Chemical	Total
1998	0	4	4	1	0	9
1999-2000	0	10	23	1	1	35
2001	0	3	22	3	3	31
2002	0	8	15	1	6	30
2003	0	11	17	2	4	34
2004	0	10	25	2	3	40
2005	0	12	23	2	1	38
2006	0	6	20	3	3	32
2007	0	11	25	2	2	40
2008	0	15	20	3	3	41
2009	0	14	20	1	7	42
2010	0	24	12	2	7	45
2011	11	21	16	5	3	56
2012	0	10	23	4	3	40
2013	0	11	29	3	5	48
2014	12	20	15	2	6	55
2015	12	17	19	2	4	54
2016	10	10	23	3	4	50
2017	19	13	20	3	3	58

In addition to the routine programme, in 2011 a pilot programme for generic medicinal products was launched. At the request of the CHMP, centrally authorised generics of clopidogrel film-coated tablets were targeted. The products were sampled by 12 inspectorates and testing was carried out by 3 OMCLs. As the outcome of this trial phase was satisfactory, a dedicated procedure was established and is initiated when generic medicines containing the same active substance are identified for testing. The aim of a generic programme is to develop and make use of a common test protocol (i.e. based on a group of methods, e.g. Ph. Eur., MAH method and/or specifically developed in-house methods) that allows for the screening of all generic versions of a medicinal product.

[1] H = Human
[2] Vet = Veterinary
[3] Imm. = Immunological

As of 2014, two generics programmes were run every year in parallel to the regular programme.

Graphic 2: Distribution of the categories of products tested each year



3) Pharmaceutical forms tested

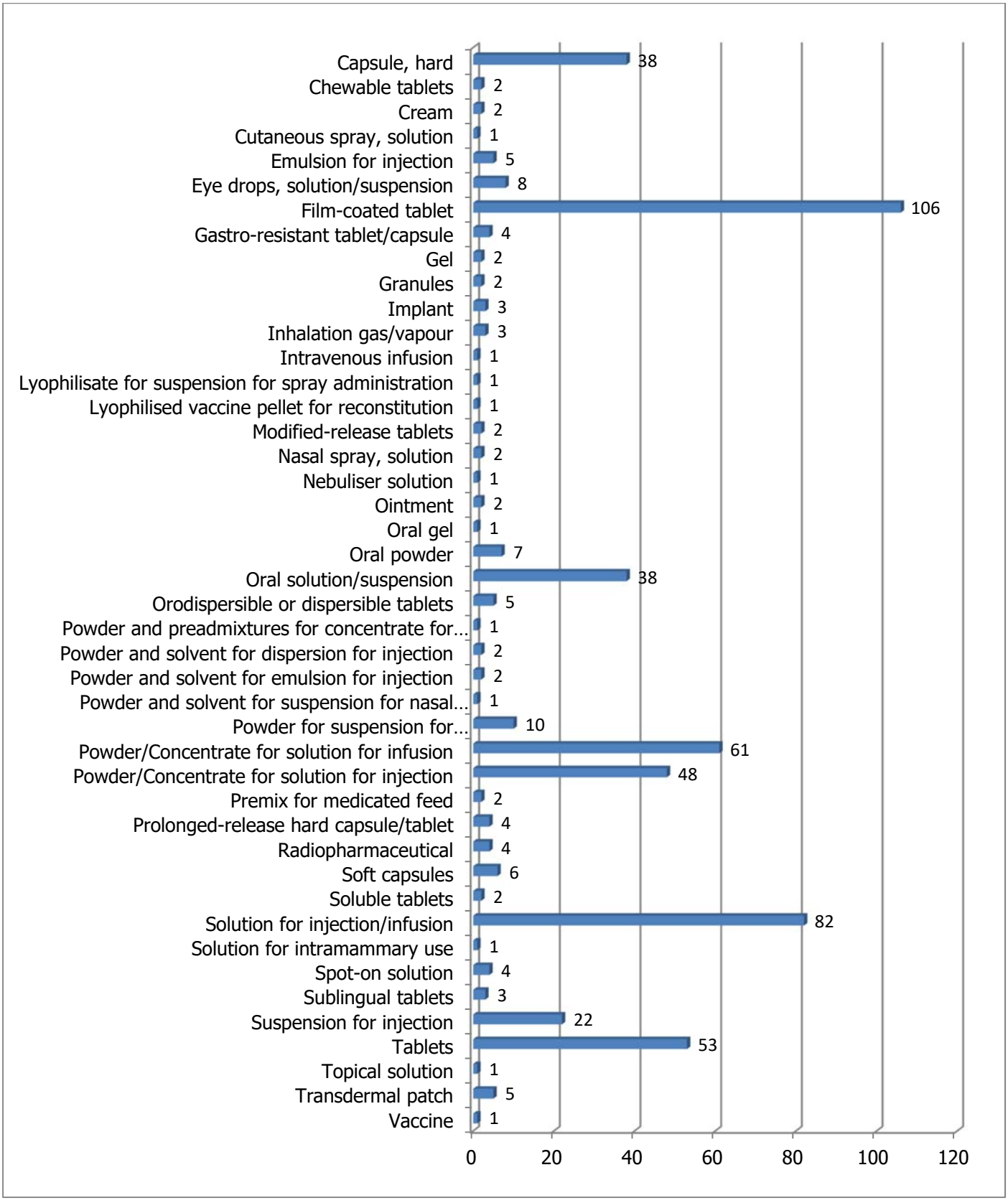
The distribution of the pharmaceutical forms tested reflects the types of forms authorised over the years via the centralised procedure. As anticipated, capsules/tablets and powder/solution/suspension for injection/infusion are the most representative pharmaceutical forms authorised and, as a consequence, tested.

Table 3: Distribution of products tested by pharmaceutical form

Pharmaceutical form	Number
Parenteral preparations	237
Oral preparations - solid forms	228
Oral preparations - liquid and semisolid forms	44
Cutaneous and transdermal preparations	17
Eye preparations	8
Preparations for inhalation	7
Oromucosal preparations	1
Others[4]	10

[4] "Others" include the following pharmaceutical forms: Implants, Powders and solvents for suspension for nasal administration, Premixes for medicated feeding stuff for veterinary use and Radiopharmaceuticals.

Graphic 3: Distribution of products tested by pharmaceutical form[5]



[5] One veterinary vaccine was tested during the trial phase in 1998.
Retested products have not been included in the figures.

3. Sampling

Samples are collected from across the distribution chain by the competent national services of, as a general rule, three EU/EEA member states: the choice of the countries is made by the EDQM taking into account climatic conditions in the different member states and with the aim of sharing the sampling workload equally among the countries. Sales volumes are also taken into consideration. The inclusion of parallel distributed CAPs in the Sampling and Testing programme is also encouraged.

The figure below illustrates the number of samples taken in each country of the EU/EEA and indicates the broad coverage of the programme with samples taken from almost all EU/EEA markets.

Figure 1: Samples taken per country

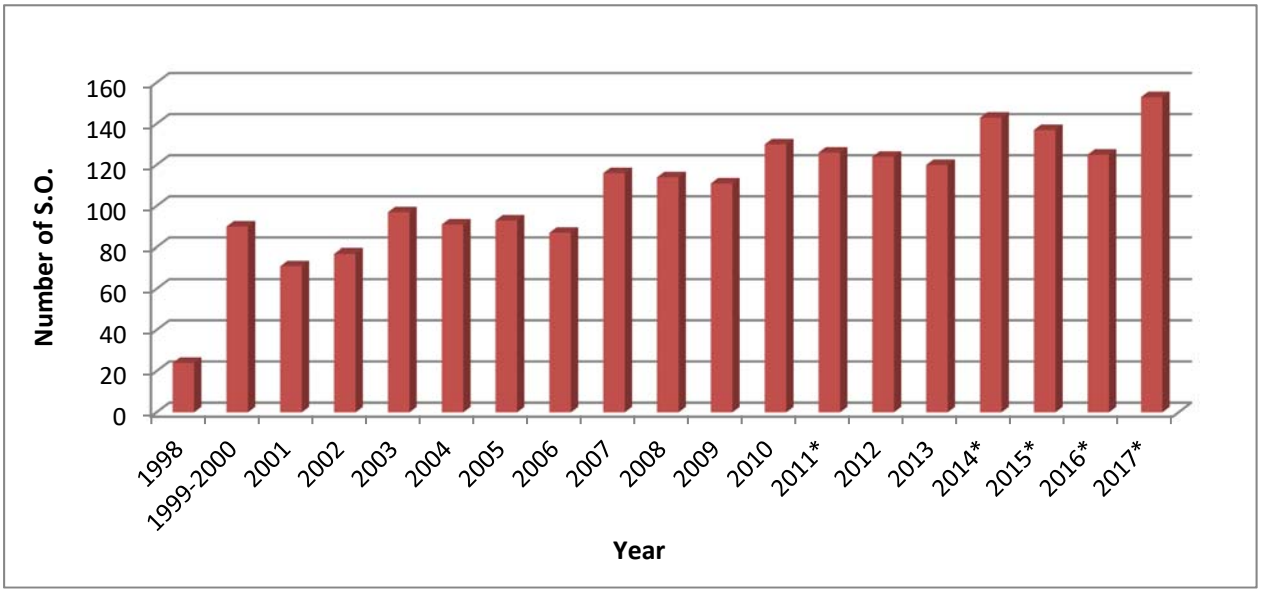
The sample size is a case-by-case decision which depends on the number of pharmaceutical dosage units needed per test procedure, the number of presentations of the dosage forms to be tested, the availability of the product, the size of the market, the clinical use of the product, etc. Within each sampling country, samples should originate from a single batch to ensure comparability and

adequacy of the results of the different tests performed. In general, market samples originate from 3 different batches (1 batch per sampling country). However, for orphan drugs or other products with restricted indication(s), the general rules may be adapted on a case-by-case basis to take into account the specific market situation (this generally leads to a reduced number of batches to be tested).

For each product, vouchers (usually 3) for rapid sample replacement are sent to the legal contact person of the MAH for return to the EDQM; by signing the vouchers the MAH commits to rapidly replace the actual quantity of pharmaceutical units sampled.

Each sampling member state chooses an appropriate site within the distribution chain on its national territory, as close as possible to the patient. Samples should preferably be drawn from a retail pharmacy or a hospital pharmacy. However, the choice of sampling location depends on the availability of the required product(s) and on the number of packs requested by the EDQM for appropriate testing in accordance with the pack size(s) available; it is also strongly linked to sampling practices and the competences of the inspectors in each member state. This explains why the majority of the samples are collected at wholesaler or MAH warehouse level.

Graphic 4: Sampling operations (S.O) performed [6]



The MAHs of the products selected are also requested to provide material (one control sample and reference testing material(s)) which are required for the testing at the OMCLs.

Since 2011, samplers have been asked to carry out checks on the printed packaging materials of the samples taken: verify the compliance of the main information on the label and in the package information leaflet (PIL) with the authorised texts. The purpose of the exercise is not to perform a comprehensive label and PIL check for compliance, but rather to highlight issues for further investigation.

[6] * including generics sampling operations

4. Testing

1) Parameters tested

The parameters to be tested are based on the recommendations from the Rapporteur and co-Rapporteur that were responsible for the assessment of the dossier. Their in-depth knowledge of the product allows them to select the most critical parameters to be tested on the finished product and, if justifiable, in addition on the active substance.

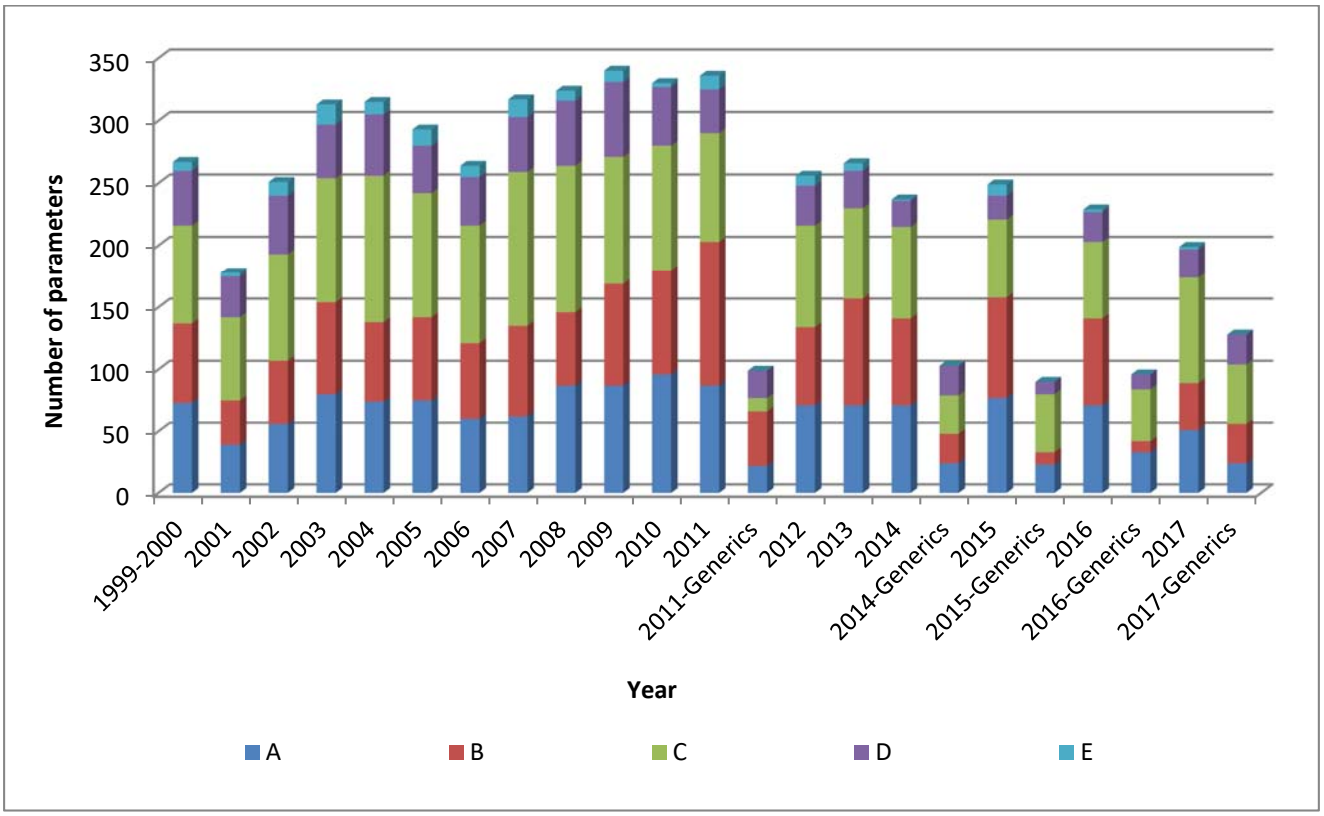
Since the beginning of the CAP programme, more than 4700 parameters have been tested in the different laboratories.

The testing parameters are classified into five different categories, as shown in Table 4. The most commonly selected test parameters are mainly focused on the assay of active substances or preservatives (Category A), on the potency of biological products and the purity of medicinal products (Category B) and on the physical/pharmaceutical characteristics of the products (Category C). Identity (Category D) and microbial/bacterial contamination tests (Category E) still continue to be requested but less often.

Table 4: Testing parameters classified by category

Category	Parameters
A	Tests related to the determination of active substance/preservatives content and potency; this also includes the tests for uniformity of content
B	Tests performed to assess the purity of the medicinal product and/or the integrity of the active substance (e.g. related substances, residual solvents, molecular size distribution)
C	All tests linked to physical/pharmaceutical characteristics (uniformity of mass, disintegration of tablets, appearance, colour, clarity); this category also includes the tests for water content, particulate matters and particle size
D	Identity tests
E	Microbial/bacterial contamination tests such as determination of bacterial endotoxins, sterility test

Graphic 5: Number of parameters tested per category per year



2) The testing phase

The National Authorities contribute to the implementation of the Sampling and Testing Programme through their involvement in the testing phase; their OMCLs provide expertise and resources for the testing of the products sampled.

The work of the OMCLs is co-ordinated by the EDQM through the OMCL Network, which includes countries that are signatories to the European Pharmacopoeia convention. A limited group within the Network (which only includes laboratories from EU/EEA countries) is involved in the testing of the Centrally Authorised Products.

The number of OMCLs to be involved in the testing of a product is defined by the product type. A distinction is made between chemical and non-chemical products (e.g. products from rDNA technology, immunological products and biological products).

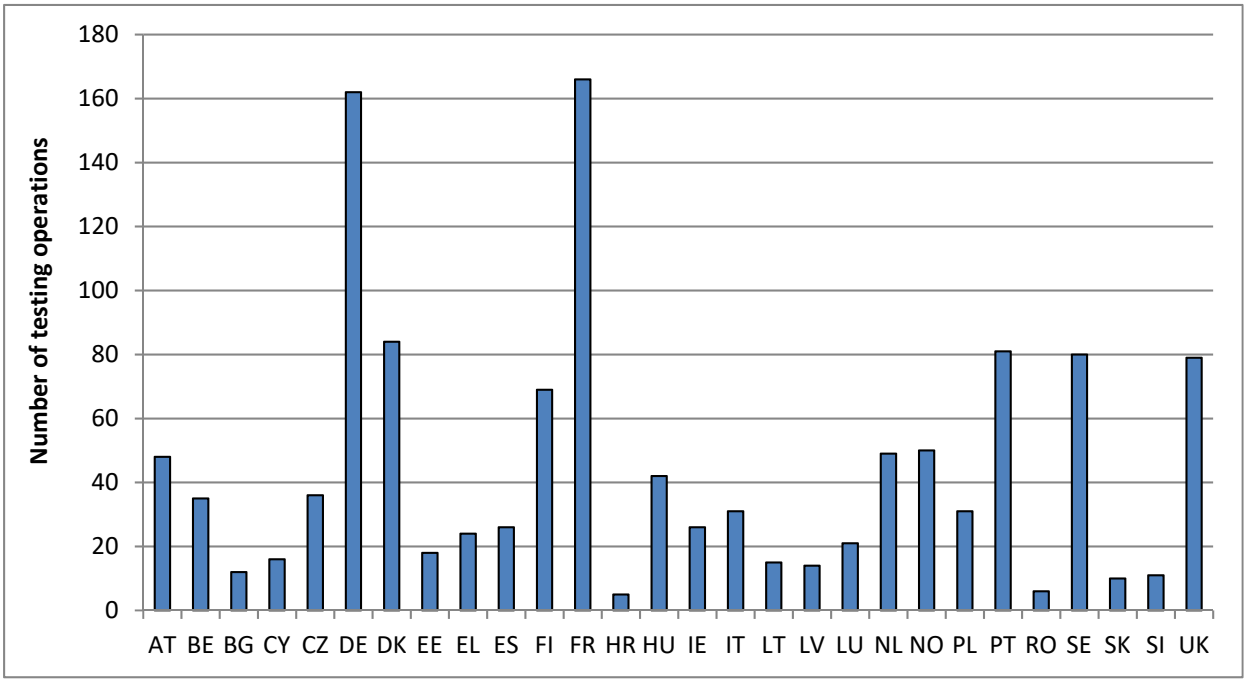
Non-chemical products are tested in two different OMCLs: this served at the beginning of the programme to ensure mutual confidence in the results among the Network members, but has since been recognised as an important way of cross-verifying the data, as the methods used for testing these products are more complex and results subject to a higher variability.

Based on the experience gained, chemical and insulin-like products are tested in a single OMCL. This testing scheme allows the economising of resources allocated to the CAP programme and the reduction of the amount of samples drawn from the market.

All OMCLs from the different EU/EEA member states are given the possibility to be involved in the CAP testing programme on a voluntary basis (bearing in mind individual technical competencies) and efforts are made to ensure that as many laboratories as possible participate in the testing phase.

The contribution of the national laboratories to the testing phase is detailed in Graphic 6 and Tables 5 and 6.

Graphic 6: Testing operations[7] on finished products carried out by national laboratories (regular and generics programmes)



Market samples, CTS and reference materials are sent to the participating OMCLs together with the approved methods from the MAH. OMCLs are not requested to fully revalidate the methods, since the validation has already been done by the MAHs. They are, nevertheless, requested to demonstrate the successful method transfer (e.g. compliance with the system suitability criteria and/or assay acceptance criteria included in the test procedures with supporting documentation, e.g. chromatograms).

The testing has to be done within a specific timeframe: 40 working days are scheduled for chemical products and 65 working days for non-chemical products. An extension of the testing period may be granted on a case-by-case basis when numerous tests are requested for a given product, when testing of the active substance is included in the testing protocol or when issues are encountered during the testing.

[7] For the statistics a "testing operation" is defined as the testing of one trade name, one pharmaceutical form and one strength (i.e. the testing of two strengths of the same product is counted as two testing operations).

Table 5[8]: Testing operations on finished products carried out by OMCLs in the regular programmes

Country	1998	1999-2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
AT	1	4	3	1	3	4	3	1	3	2	2	1	1	1	6	4	1	2	2
BE	0	3	3	3	3	1	2	2	2	3	1	2	3	1	1	2	1	1	1
BG	0	0	0	0	0	0	0	0	0	1	1	3	0	1	2	1	1	1	1
CY	0	0	0	0	0	1	1	2	1	1	1	1	1	2	1	1	1	1	1
CZ	0	0	0	0	0	1	1	3	2	2	2	2	1	3	2	2	2	2	4
DE	4	11	9	8	7	11	13	8	5	10	5	7	8	9	7	5	11	6	6
DK	1	8	6	6	9	4	4	4	5	4	4	3	4	4	4	3	5	2	4
EE	0	0	0	0	0	0	0	1	1	1	1	1	2	1	1	1	0	1	1
EL	0	4	4	2	1	2	0	1	1	2	1	1	0	1	1	0	1	1	1
ES	1	2	2	1	2	3	1	1	0	0	1	1	0	1	2	1	1	1	1
FI	1	5	5	4	6	5	4	2	3	3	4	4	5	3	3	3	4	3	2
FR	6	10	8	8	11	12	8	5	6	7	6	4	9	8	10	8	3	6	7
HR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2	1
HU	0	0	0	0	0	1	1	2	2	3	2	3	4	4	5	3	3	2	3
IE	0	1	0	3	2	0	1	4	1	3	1	1	1	2	2	1	1	1	1
IT	1	2	3	2	2	2	5	2	1	1	1	1	2	1	2	1	0	1	1
LT	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	3	1	1	1
LV	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	1	1	2
LU	1	1	1	1	1	2	1	1	1	1	1	1	0	1	1	1	1	0	0
NL	3	3	6	3	2	4	3	3	2	4	2	3	1	1	2	2	2	2	1
NO	0	1	1	5	3	3	2	3	1	2	2	2	4	5	3	1	3	3	3
PL	0	0	0	0	0	1	3	7	2	2	2	1	1	1	3	1	3	2	2
PT	0	3	4	4	7	9	4	6	4	2	4	5	4	4	3	4	4	3	3
RO	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	2	0	1
SE	1	6	5	4	10	6	4	4	5	6	5	3	5	3	3	2	4	2	2
SK	0	0	0	0	0	1	1	1	1	0	0	0	0	2	1	1	1	1	0
SI	0	0	0	0	0	1	2	1	1	1	0	1	0	1	1	1	0	0	1
UK	4	8	4	8	6	6	5	5	3	2	3	3	3	1	4	4	3	2	1

[8] In Malta, Liechtenstein (EEA) and Iceland (EEA) there are no national OMCLs.

Table 6[9]: Testing operations on generic products carried out by OMCLs

The lead molecule for each generics programme is indicated in the table below.

For each programme, a scientific advisor is nominated; numbers in **bold** type indicate that the scientific advisor came from the corresponding member state.

	AT	BE	BG	CY	CZ	DE	DK	EE	EL	ES	FI	FR	HU	IE	IT	LT	LV	LU	NL	NO	PL	PT	RO	SE	SK	SI	UK
2011 Clopidogrel	/	/	/	/	/	3	/	/	/	/	/	**6**	/	/	/	/	/	4	/	/	/	/	/	/	/	/	/
2012	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
2013	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
2014 Pramipexole	/	/	/	/	/	/	/	/	/	/	/	**3**	/	/	/	/	/	/	/	3	/	/	/	/	/	/	/
2014 Telmisartan	/	/	/	/	/	5	/	**3**	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
2015 Irbesartan	/	/	/	/	/	/	/	/	/	**4**	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	2
2015 Temozolomide	/	/	/	/	/	/	/	/	/	/	/	**4**	4	/	/	/	/	/	/	/	/	/	/	/	/	/	/
2016 Repaglinide	/	/	/	/	/	/	/	3	/	/	/	**4**	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
2016 Leflunomide	3	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	**3**
2017 Zoledronic acid	/	/	/	/	/	**4**	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	4	/	/	/	/	/
2017 Meloxicam	/	/	/	/	**7**	/	/	/	/	/	/	7	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/

[9] In Malta, Liechtenstein (EEA) and Iceland (EEA) there are no national OMCLs.

3) Testing outcomes

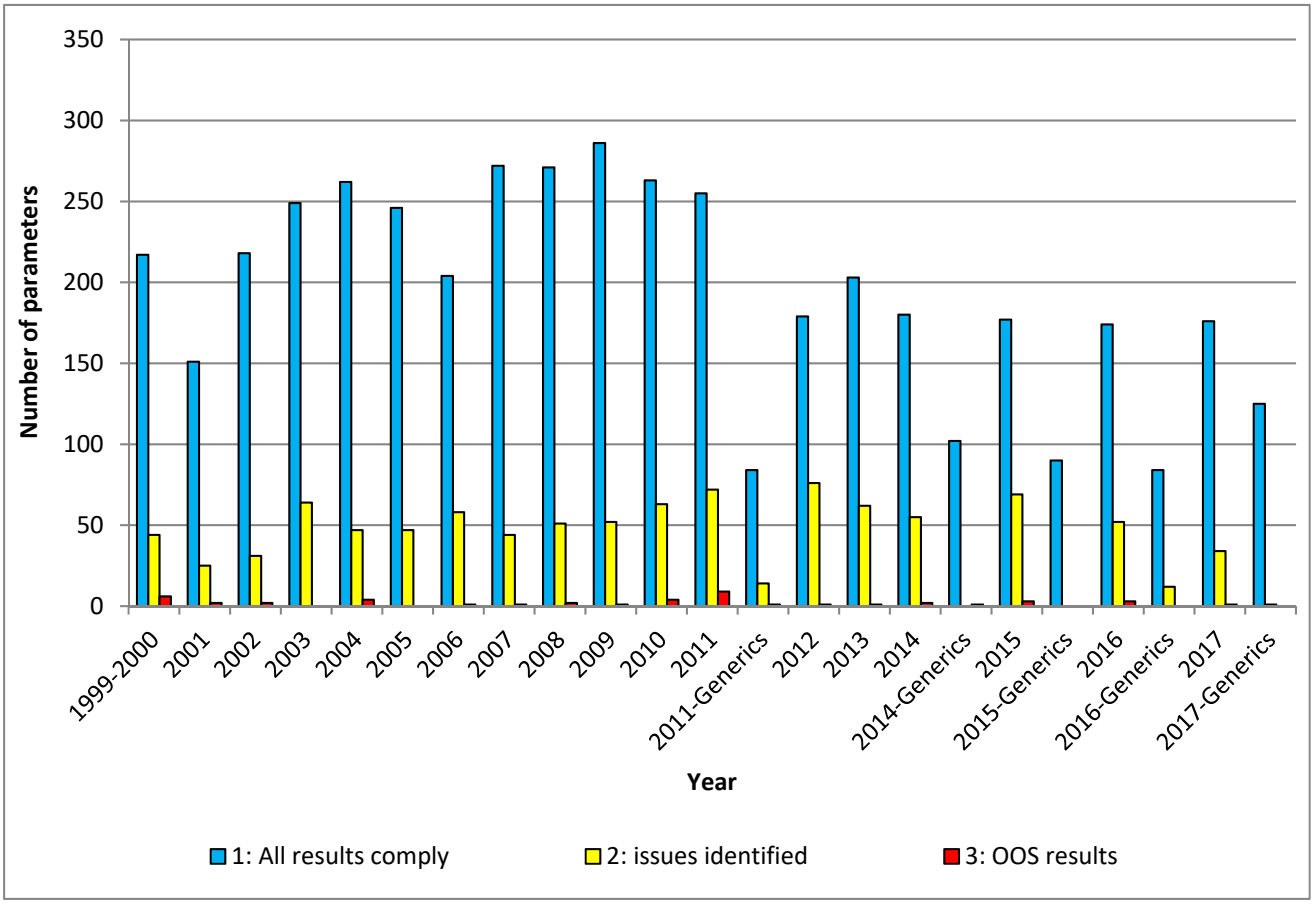
For each product, the EDQM sets up a CAP Testing Report (CTR) which it distributes to the EMA, all OMCLs and the participating samplers. The EMA forwards the CTR to the MAH and to the Rapporteur and Co-Rapporteur, where deemed necessary. The EMA has the responsibility for follow-up actions as an outcome of the testing.

In order to better structure the final outcome of the testing, it was agreed to classify the testing results according to the following three options:

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

As illustrated in the comparative graph (See Graphic 7), products available on the EU/EEA market and the methods used to control them (as indicated in the MAHs' marketing dossiers) are, generally speaking, of good quality. Nevertheless, issues were still encountered in a significant number of cases, thereby underlining the need for independent testing.

Graphic 7[10]: Testing results according to the above-mentioned classification scheme



[10] The outcomes of all testing parameters for all products have been taken into account.

Most of the problems identified during the testing were dealt with through communication and clarification involving (depending on the issue) the MAHs, the EMA 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 (where needed, through variations).

In other cases, especially when problems of compliance with the quality specifications had been identified, other regulatory actions (Quality Defect procedure, retesting, inspections, etc.) were deemed to be necessary. To date, four batch recall procedures have been initiated:

- One in 2006 because the appearance of Somatropin injection preparation was not compliant with the specifications.
- One in 2009 because the total impurities content of a veterinary antibiotics was not compliant with the specifications.
- Two in 2017 because the content of an unknown impurity in a Zoledronic acid generics and the pH value of a Meloxicam generics were not compliant with the specifications.

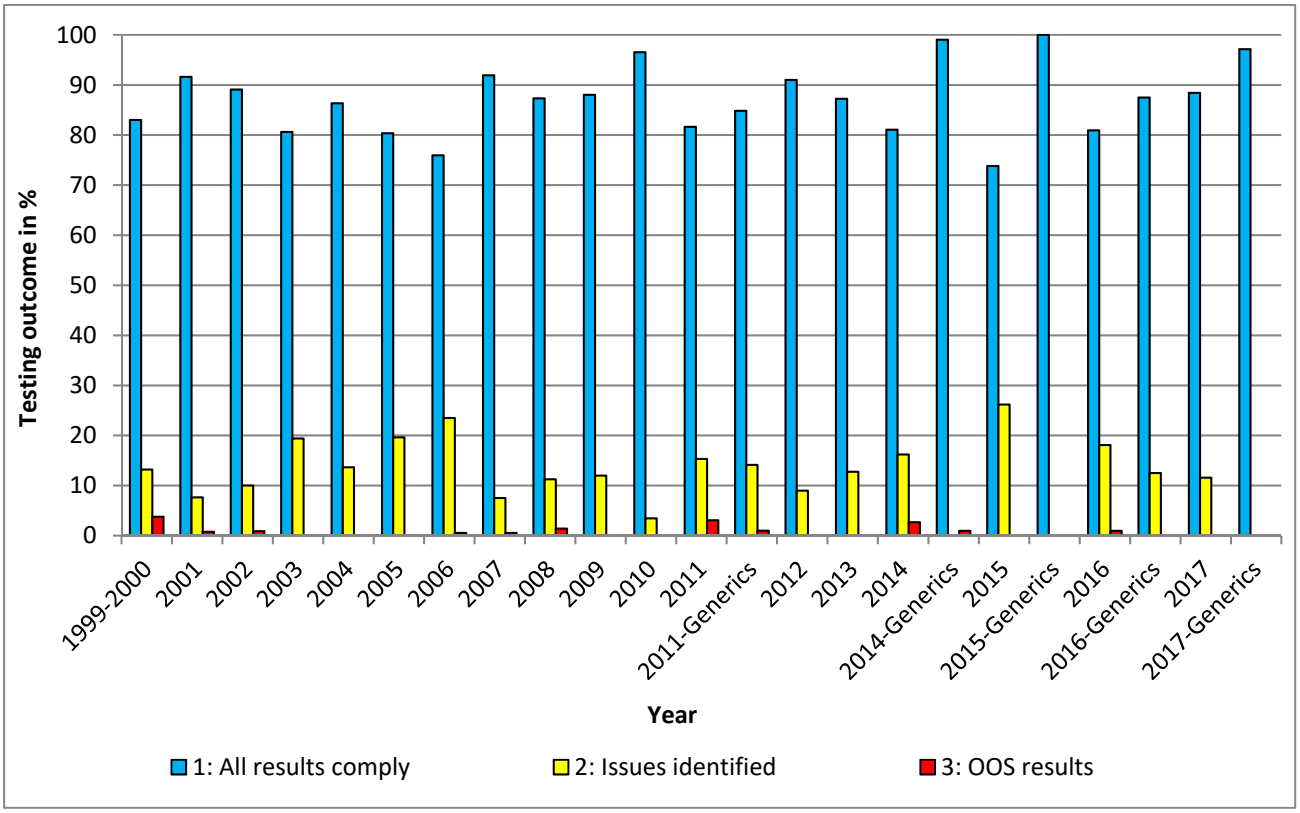
Regarding the problematic issues encountered, it should be noted that with respect to the number of products tested per product type, the parameters showing technical/scientific or regulatory issues, were distributed as follows:

- 9% of the total number of parameters tested for Human Chemical Products;
- 9% of the total number of parameters tested for Veterinary Chemical Products;
- 18% of the total number of parameters tested for Human Biological Products;
- 25% of the total number of parameters tested for Veterinary Immunological Products.

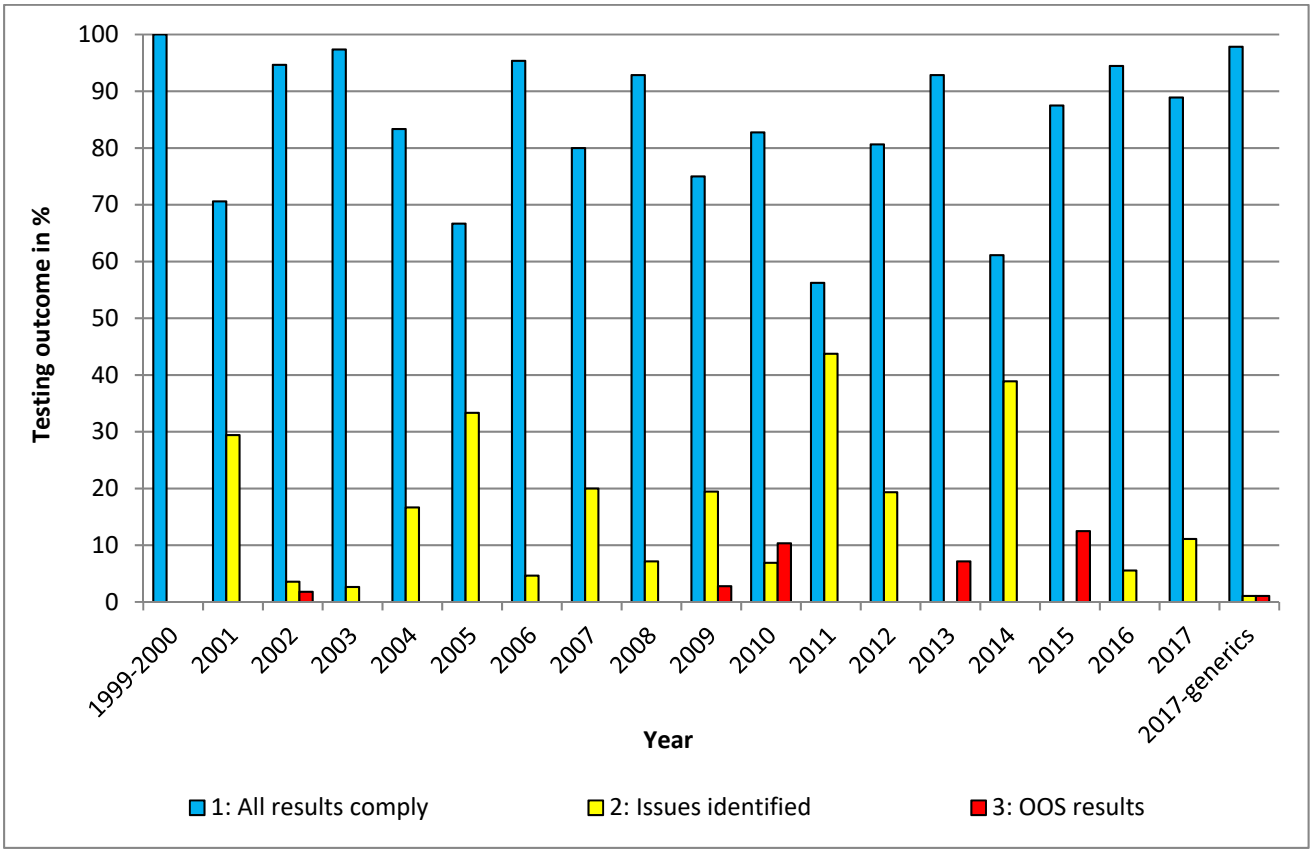
Results are similar for human and veterinary chemical products. This is linked to the fact that the techniques and methods used are the same and are, in general, well established. For human biological products, the higher level of major technical/scientific or regulatory issues might be linked to the fact that the products are more complex and as a consequence the test methods involved are usually more sophisticated and sensitive.

In general, more issues were encountered for Veterinary Immunological Products than for Human Biological Products. According to the feedback from the testing OMCLs, the SOPs in the veterinary field are often less detailed and require additional clarification by the MAH.

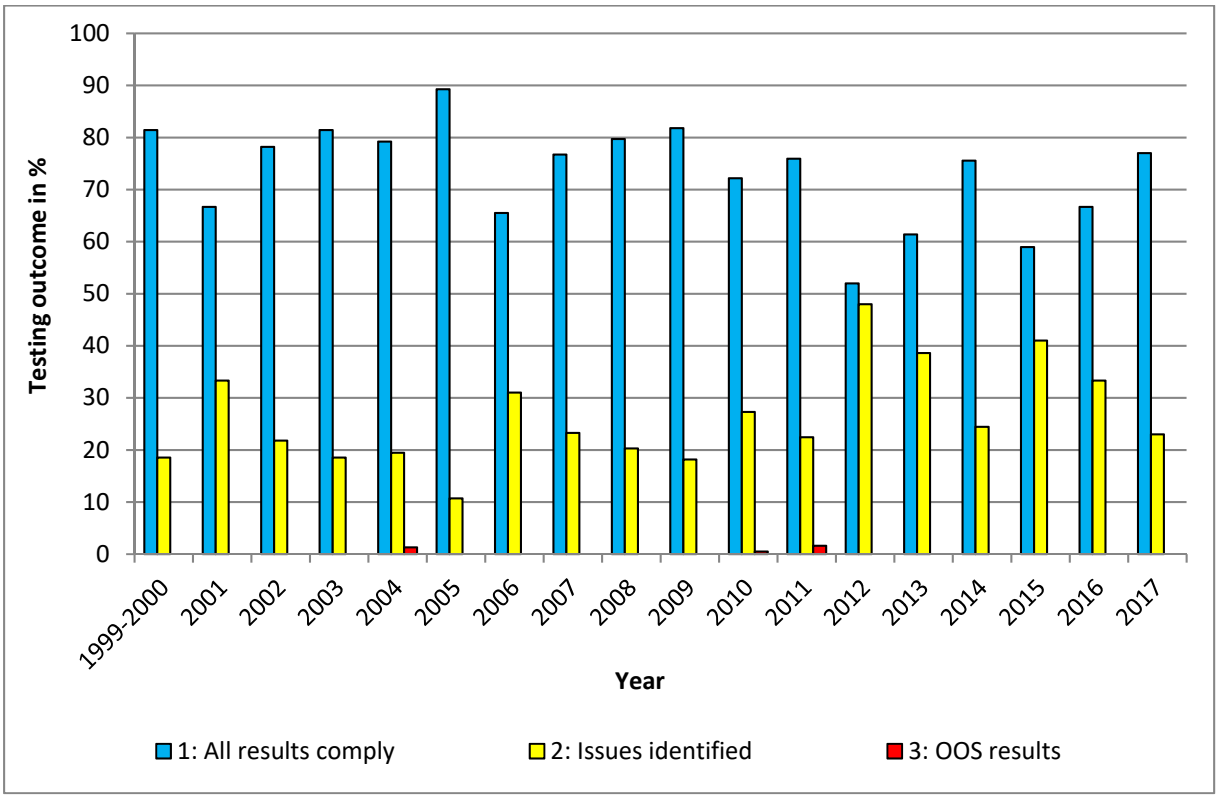
Graphic 8: Testing outcomes for Human Chemical products (not considering OOS leading to recalls)



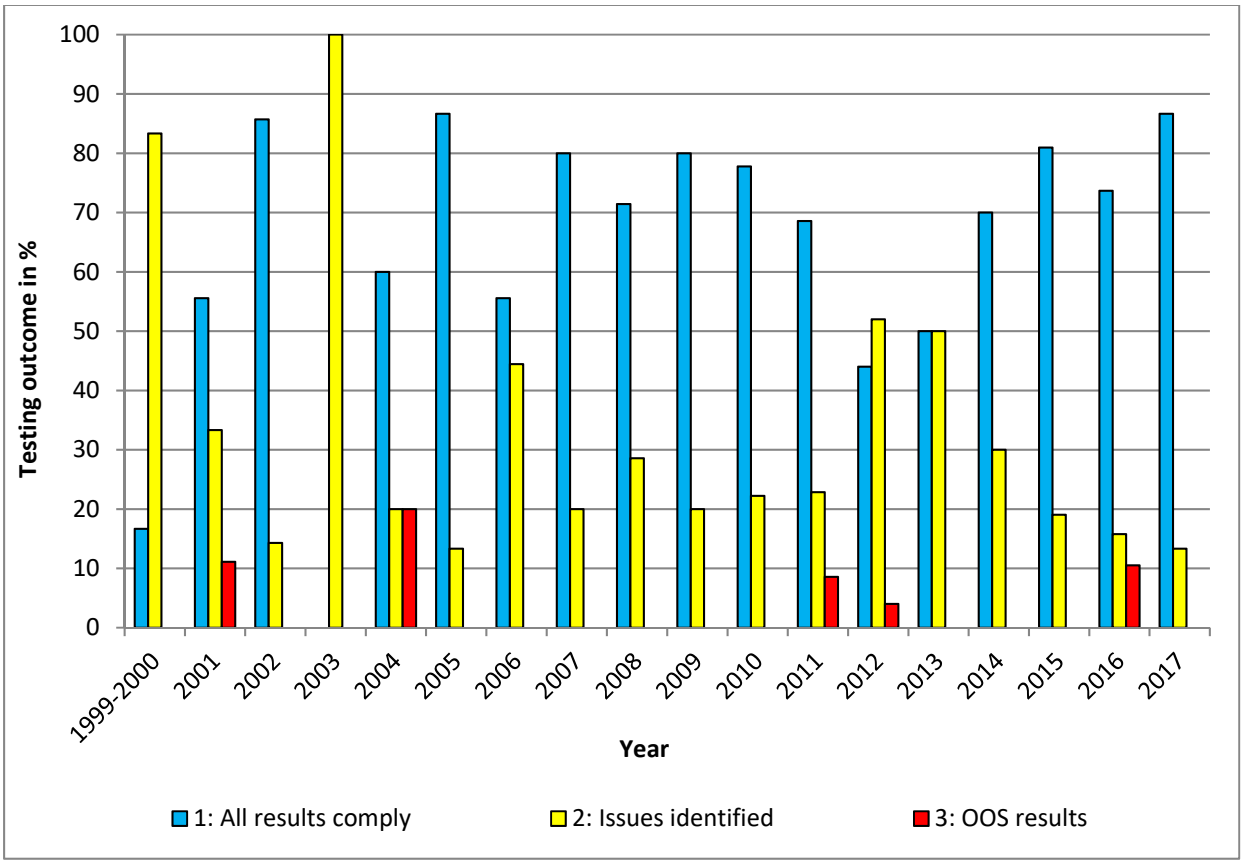
Graphic 9: Testing outcomes for Veterinary Chemical products (not considering OOS leading to recalls)



Graphic 10: Testing outcomes for Human Biological products (not considering OOS leading to recalls)



Graphic 11: Testing outcomes for Veterinary Immunological products (not considering OOS leading to recalls)



5. Benefits

The purpose of the CAP programme is to supervise the quality of the centrally authorised medicinal products that are placed on the EU/EEA market, in all parts of the distribution chain, by testing their compliance with their authorised specifications. In addition, testing OMCLs check that the authorised control methods are suitable for their intended use.

The networking effect of expertise serving both authorities and manufacturers is an independent tool which benefits European citizens. Work-sharing based on a commonly agreed quality standard (ISO 17025) fosters mutual recognition between OMCLs of the EU/EEA OMCL Network and favours the development of centres of excellence. The programme relies on an efficient network of competent and dedicated experts, who agree to share the work and responsibilities, and offer their expertise by contributing synergistically to this programme. With the resources available in the Network, efficient market surveillance by testing becomes possible.

There are multiple benefits to developing a common approach for post-marketing control of products authorised through the centralised procedure. The main outcome of the programme is the provision of independent quality control and, as a consequence, the guarantee of a high quality level of CAP products on the EU/EEA market.

For the EMA, EDQM, NCAs and their OMCL(s), the programme facilitates the sharing of the surveillance workload and avoids the duplication of efforts. The programme reduces unnecessary duplication of regulatory sampling and testing by replacing individual national systems for the testing of centrally authorised products with one harmonised surveillance procedure applicable to all EU/EEA member states under the responsibility of one co-ordinating body.

This collaborative exercise ensures the pooling of expertise, laboratory capacity and human resources throughout the EU/EEA OMCL Network, while providing access to novel technology and selective analytical methods. The programme facilitates the best use of laboratory resources and expertise in emergency situations, such as when quality defect issues arise.

6. Outlook

Looking to the future, it is important that the competencies and infrastructure that are required to allow a comprehensive, independent and modern surveillance programme, based on the principles of work-sharing, risk management and optimisation of laboratory resources and capacities, are maintained.

The year 2019 marks the beginning of a new approach to CAP Sampling and Testing. In 2017, the EMA began working with the EDQM and the CAP Advisory Group to further expand the Sampling and Testing Programme. As part of this expansion, improvements to the current sampling and testing arrangements, as well as new CAP market surveillance projects, will be introduced:

a. Testing more biological products

The EMA has pointed out in recent years that the number of biological products tested was too low and had not increased since 1999, while the number of authorised CAP biological products has increased.

Usually, 15 to 20 biological products are tested every year (including insulins) which is in line with the current capacity of the Network; according to the adopted testing scheme, each biological product is tested in 2 OMCLs. In order to increase the coverage of biological products, due to limited testing resources, improvements to the testing scheme have been made and their implementation will be reviewed and further discussed in the coming years.

b. Biosimilar programme

The number of authorised biosimilar products has also been increasing; therefore in 2014 the possibility of running a programme on CAP Biosimilars, applying similar principles to those for the generics programme for chemicals, was discussed at the level of the CAP Advisory Group.

Filgrastim-containing products were selected for a pilot study as several of these products had already been tested within the CAP programme. A dedicated group of volunteers from the Network started with a comparative study of the manufacturers' testing methods and the Ph. Eur. monograph *Filgrastim concentrated solution (2206)* (which covers the drug substance), and it was ultimately decided to continue with a feasibility study. The practical details for the work sharing of the parameters and the samples needed for this feasibility study were elaborated at the beginning of 2015.

The conclusions of the feasibility study were positive and a detailed testing protocol was prepared so that market samples could be tested in a future routine programme. As such, a biosimilar programme has been included in the next co-operation agreement between the EDQM and the EMA and three projects will be conducted over a period of five years (2019-2024).

c. Parallel distribution

Over the years, many ways to increase the number of samples in the CAP Sampling and Testing Programme taken from the parallel distribution chain have been explored. A new strategy, that takes into account the specifics of the parallel distribution market, has been included in the next co-operation agreement between the EDQM and the EMA. This will take the form of a stand-alone testing programme, independent from the products selected for the general annual CAP programme. As part of this tailored programme, samples of centrally authorised products will be randomly taken from the parallel distribution chain and tested to verify their authenticity. Testing will focus on authenticity, with the possibility to include other parameters, if needed.

d. Generic programme

After an EMA request to enlarge the yearly turnover of tested CAP Generics, options to combine the CAP Generics and the MRP/DCP programmes were proposed by the EDQM. This has led to the development of an alternative concept for future CAP Generics test programmes.

The new approach to the Generic Programme aims to create synergies with Sampling and Testing Programmes conducted by the OMCL Network for national and MRP/DCP products, and to increase the coverage of market surveillance. This new approach will become operative as of 2019 with 3 generic projects covering INNs (International Non-proprietary Names), for which testing experience already exists within the OMCL Network, planned to be conducted every year during the period from 2019 to 2023.

e. API Testing programme

In order to have a better overview of the quality of Active Pharmaceutical Ingredients (APIs) and leveraging sampling and testing and GMP inspections of API manufacturing sites, an ad hoc CAP API programme will become part of the next co-operation agreement between the EDQM and the EMA, allowing the testing of APIs sampled during GMP inspections.

f. HMA (Heads of Medicines Agencies) initiatives on a Risk-based Approach for the selection of Medicinal Products for Surveillance Testing

In many NCAs the same quality assessors assess CAP, MRP and DCP products. In order to ensure maximum efficiency and consistent interpretation, a single template for the assessors' feedback to OMCLs concerning proposed test parameters and a global model for the identification of risks associated with medicinal products across all authorisation procedures is being developed by an HMA multi-disciplinary working group. The new risk-ranking model, which will support the planning of post-authorisation surveillance sampling and testing programmes for all newly authorised products (CAPs, MRPs, DCPs and national products, if applicable), is envisaged to be incorporated into the EMA risk-based selection model for CAPs in the future.

7. Conclusions

The Sampling and Testing Programme remains an important tool to ensure that the quality of Centrally Authorised Products (CAPs) placed on the EU/EEA market meet the expected requirements, and that MAHs operate in compliance with the legislation and in line with the information available to authorities in registration files. In addition, the programme allows the sharing of the workload within the member states, resulting in time and resource savings for all stakeholders.

Starting in 1998 with a trial phase involving nine products, the Sampling and Testing Programme has developed into one of the key tools for monitoring the quality of centrally authorised products, including innovative biologicals, available on the European market.

Between the years 1998 and 2017, more than 700 products were tested, which represents 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 medicines authorised through the mutual recognition and decentralised procedures.

The benefits of market surveillance testing were recently highlighted when confirmed out-of-specification results were found for an unknown impurity during the Zoledronic acid CAP generics testing campaign. A quality defect procedure was launched, followed by the identification of GMP non-compliances impacting several products at the manufacturing site (i.e. confirmed cross-contamination).

The programme relies on the positive and constructive co-operation between all partners involved (EMA, EDQM, MAHs, National Inspectorates/nominated sampling contact persons and testing OMCLs of the Network). The suggestions and advice provided to the EMA by the national competent authorities, which operate similar projects on national levels, have certainly helped to develop and refine the programme over the years.

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