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Inspections and Human Medicines Pharmacovigilance Division

Results of the sampling and testing programme for the year 2014

Human and veterinary products

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5525
Send a question via our website www.ema.europa.eu/contact

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Glossary

API:	Active pharmaceutical ingredient (active substance)
CAP:	Centrally authorised product
CHMP:	Committee for Medicinal Products for Human Use
CVMP:	Committee for Medicinal Products for Veterinary Use
DCP:	Decentralised Procedure
EDQM:	European Directorate for the Quality of Medicines and HealthCare
EMA:	European Medicines Agency
EEA:	European Economic Area, formed by the Members of the European Union and Iceland, Liechtenstein and Norway
MAH:	Marketing Authorisation Holder
MRP:	Mutual Recognition Procedure
NAP:	Nationally authorised products
NCA:	National competent authorities
OMCL:	Official Medicines Control Laboratory
OOS:	Out of specification
PIL:	Package Leaflet
SOP:	Standard Operating Procedure

1. Executive summary

This report describes the results of the 2014 sampling and testing programme coordinated by the European Medicines Agency (hereinafter "the Agency").

A total of 47 centrally authorised products (CAPs) were sampled from the European Economic Area market and tested; the selection of the products followed a risk-based approach[1]. Most of the products tested complied with their authorised specifications. Batches from two human products were found to be out of specification and, in both cases, a quality defect procedure was initiated. A Class II recall for one batch of one product was carried out. Furthermore, checks of the printed packaging materials of the sampled products were carried out in order to verify potential non-compliances from the details in the marketing authorisation.

In one case, one batch was recalled (Class III recall) from the market. In another case a GMP Inspection of the manufacturer was triggered as a result of the test results of the medicinal product; in 3 cases, variations were needed to update the registered test methods.

Six active substances were also sampled and tested, and they all complied with their specifications.

The results are summarised in the tables below.

Table 1. Centrally authorised products (CAPs) tested in 2014

Number products tested	Number of OOS / QD	Number of recalls	Number of inspections	Number of variations
47	2	2	1	3

Table 2. Active pharmaceutical ingredients (APIs) tested in 2014

Number API's tested	Number OOS / QD	Number of Recalls	Number of Inspections	Number of Variations
6	0	0	0	0

The sampling and testing programme[2] is a valuable tool that allows the Agency to monitor the quality of centrally authorised products available on the EEA market. These results show the benefit of the risk-based approach in the selection of products.

[1] Risk-based approach
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500005114.pdf

[2] Sampling and testing webpage
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000174.jsp&mid=WC0b01ac058002708d

2. Introduction

The Agency co-ordinates the sampling and testing programme each year in accordance with Art. 57 (r) of Regulation (EC) 726/2004[3]. This monitoring activity allows the Agency to verify that the centrally authorised medicinal products available on the market comply with their authorised quality specifications. In addition, it enables the Agency to check that the analytical methods which the manufacturers use for the control of products are satisfactory, and that they can be utilised by independent laboratories to verify the quality of the medicinal products.

The success of the programmes is based on the cooperation and partnership of the following:

- European Medicines Agency (EMA) - overall management (and risk-based approach selection)
- European Directorate for the Quality of Medicines and HealthCare (EDQM) - coordination of the sampling and of the testing, and reporting to EMA
- Network of Official Medicines Control Laboratories (OMCLs) in the EEA - testing
- Inspection Services of the EEA National Competent Authorities - sampling from the market
- EMA Scientific Committees (CHMP and CVMP) - adoption of the programmes
- Products' rapporteurs and co-rapporteurs - advice on testing recommendations and follow-up actions

The report provides information on the procedural aspects of the programme 2014 and the test results.

3. The sampling and testing programme 2014

3.1. Preparatory work

The list of products to be tested was prepared by the Agency on the basis of a risk-based approach. This approach allows the Agency to prioritise testing of products on the basis of their characteristics and use, and at the same time to make a better, more effective use of limited testing resources.

The list was adopted by the CHMP and the CVMP in February 2013.

3.2. Sampling

Samples of the products were taken by inspectors/samplers of the national competent authorities from their respective markets. When possible, each product was sampled in three different Member States.

Below is a table summarising the sampling phase.

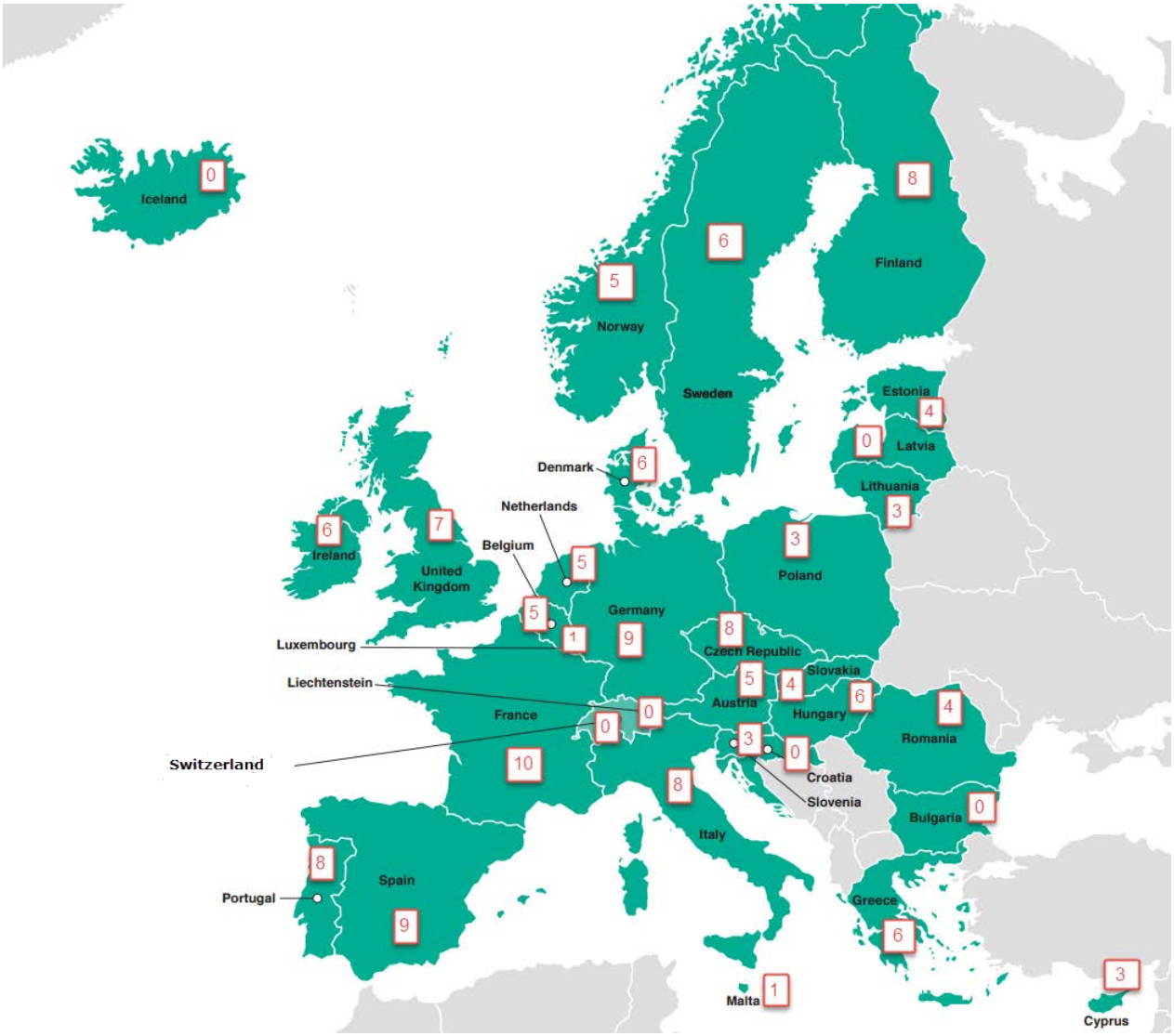
Table 3. Sampling

Number of products	Number of inspectorates	Number of samples taken
47 (39 human, 8 veterinary)	34	143

[3] Regulation European Parliament and Council
http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf
http://ec.europa.eu/health/documents/eudralex/vol-1/index_en.htm

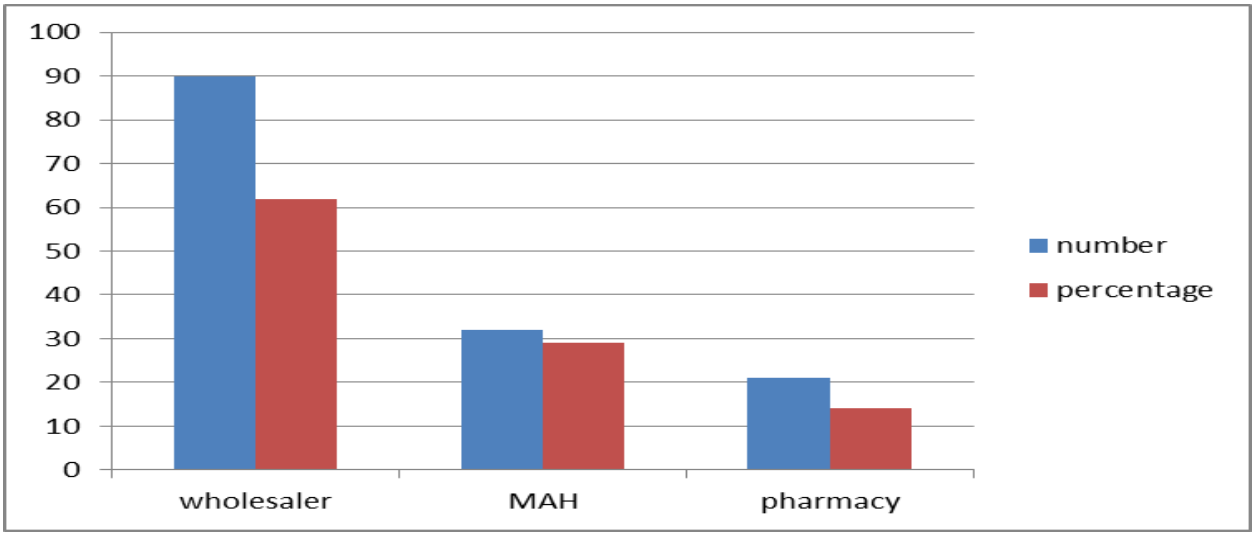
The figure below illustrates the number of samples taken in each country of the EEA and indicates the broad coverage of the programme with samples taken from almost all EEA markets. The choice of the countries is made by the EDQM taking climatic conditions of the different Member States into account and with the aim of sharing the sampling workload equally among the countries. Sales volumes are also taken into consideration.

Figure 1: Samples taken per country



The figure below shows the distribution of samples within the supply chain. Predominantly samples are taken from wholesalers due to logistical reasons.

Figure 2: Samples from supply chain



3.3. Testing

Normally, medicinal products were tested in one laboratory only, except for biological and veterinary immunological products that were tested in two laboratories. The number of products and APIs tested in Tables 4 and 5 include the products selected for the generics programme (see Section 3.4).

Table 4. Testing phase

Number of products tested	Number of laboratories
47	36

Table 5. Active substances (APIs)

Number of active substances tested	Number of laboratories
6	9

3.4. Generics programme

The Agency and EDQM, in collaboration with the OMCL network have established a specific research project to be initiated when generic medicines are identified for testing. This project seeks to develop and make use of a common test procedure (i.e. based on a group of methods, e.g. Ph.Eur, MAH method and/or specifically developed in-house methods) that would allow for the rapid testing of all generic versions of a medicinal product regardless of route of authorisation. In 2014, generics of Telmisartan and Pramipexole were selected for this programme. A total of 9 CAPs and 12 batches of APIs were sampled and tested.

Molecule	CAP: number of products tested	CAP: samples of API tested
Telmisartan	5	8
Pramipexole	4	4
Total	**9**	**12**

3.5. Label and package leaflets checks

Checks on labels and package leaflets (PIL) were carried out by the samplers using a checklist prepared by the Agency and the EDQM in order to assist in this process. The labels and PILs of the samples taken from the market were examined by the samplers to highlight potential issues requiring further investigation.

4. Results

Testing results were classified in a 1 – 3 scale, according to the testing outcome.

1 = results comply with the authorised specifications / no issues found

2 = results comply with the authorised specifications but issues of scientific, editorial or regulatory nature were identified

3 = results are outside of the authorised specifications and are non-compliant

4.1. Testing

Below is a series of tables summarising the results of the programme:

Table 6. Finished products test results

Product type	Products tested	1: Compliant / No issues identified	2: Compliant / Issues of scientific editorial or regulatory nature identified	3: Non compliant / Out of specification
Human	39	23	14	2
Veterinary	8	1	7	0
Total	**47**	**24**	**21**	**2**

There were 2 out of 47 products tested that were found to be out of specification.

There were 21 products for which issues of scientific, editorial or regulatory nature were identified.

For 3 products these issues were addressed through the submission of a variation; for 5 products there was the need to make some amendments to the testing documentation e.g. SOPs but did not require submission of a variation.

Table 7. Active substances

Active substances tested	1: Compliant / No issues identified	2: Compliant / Issues of scientific editorial or regulatory nature identified	3: Non-compliant / Out of specification
4	2	2	0

All API's tested (the table above doesn't include APIs of generics) complied with their specification.

For 2 API's tested there was the need to make some amendments to the testing documentation e.g. SOPs but did not require submission of a variation.

Table 8. Generics

Molecule	CAP: number of products tested	CAP: samples of API tested
Telmisartan	5	8
Pramipexole	4	4
Total	**9**	**12**

In addition to the 9 centrally authorised products tested within the generics programme, the common test method was also used for the testing of generics programme.

4.2. Label checks

Table 9. Labels

Labels checked	Further investigation was required	Non-compliant	Recall
116	60	4	1

5. Discussion

5.1. Testing of finished product

The data reported in Table 6 demonstrates that 45 out of 47 products tested complied with their authorised specifications and two products were found to be out of specification (OOS).

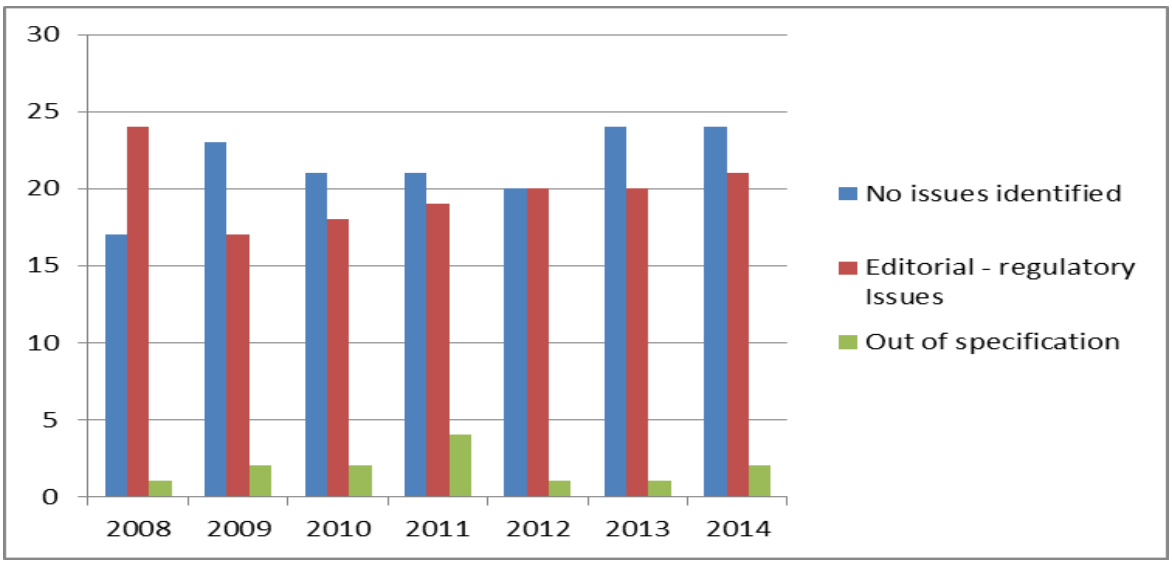
The Agency co-ordinated a quality defect procedure for the first OOS and the affected batch was recalled as a precautionary measure from hospitals and pharmacies. The recall was classified as Class II. The MAH submitted a report to the Agency outlining their investigation and corrective/preventive actions. As part of the assessment, a GMP inspection of the manufacturing site was carried out confirming that the manufacturer's investigation was performed correctly and that the corrective and

preventive measures were appropriate. Following the rapporteur's assessment and the inspection by the supervisory authority, the procedure was closed.

The Agency co-ordinated a quality defect procedure initiated for the second OOS case. The root cause investigation found that the problem might be due to the preparation of samples in the testing laboratories, rather than to the product non-compliance, and this finding was accepted by the rapporteur. No recall was necessary.

The results of the 2014 programme broadly reflect those obtained in previous years, as illustrated in the comparative graph below (Figure 3); this shows that most products comply with their authorised specifications, with only a limited number found to be out of specification.

Figure 3: Outcome of sampling & testing 2008–2014



However, the outcome of the testing performed by the OMCLs suggests that the description of the testing methods is not always adequate and more attention should be paid by the MAH and manufacturers to these methods, to ensure that the registered methods are properly described and to allow testing to be carried out by an independent laboratory.

5.2. API testing

The aim of the sampling and testing programme is to verify the compliance of the finished products with the registered specifications. Occasionally, the rapporteurs can recommend also the testing of the active substance. This is usually limited to checking the impurities when there is a justified reason (e.g. potential safety problems with impurities arising from the process). In the 2014 programme, testing of the active substance was recommended for 4 products; testing focussed on impurities and, in one case, on the identity of the active substance. In all cases the samples met the specifications (Table 7).

5.3. Generic programmes

In 2014, the Agency implemented two generic programmes to develop a common test procedure: one for generics of Pramipexole and one for generics of Telmisartan; a total of 9 CAPs and 12 API samples were tested. In addition, the OMCL network tested 106 different finished products (tablets) and 49 samples of APIs, using the same methods. In total the common test procedure facilitated the testing of 115 generic products and 61 API samples in 2014, allowing for a broad and rapid survey of a large number of generic medicines (table 8).

5.4. Product literature check

Product literature checks are performed by the samplers on the primary and secondary packaging of the samples taken. In addition, they verify that the PIL is the correct one for the sample (correct language and product). The results of the checks are summarised on a checklist which is sent to the Agency. A total of 116 checklists were received, and for 60 labels/PILs some additional investigation was required. Four labels/PILs were non-compliant and a quality defect procedure was initiated by the Agency for each one. For one of the products, a class III recall (table 9) was initiated.

6. Conclusions

Most of the products tested in the 2014 programme were in compliance with their authorised specifications, with two human products found to be outside their specifications. In one case, a batch was recalled from the market and a GMP inspection was carried out.

The results of the 2014 programme are in line with the results of previous years' showing that, at least for the batches sampled, products are consistently of the expected quality (figure 3). These results also highlight the benefits of testing performed by national laboratories for the continuous improvement of the testing methods. However, there are still shortcomings in relation to the test methods documentation and to the labelling. MAHs and manufacturers should ensure that their analytical methods and product labelling are properly documented and clearly written, and that the relevant documentation is regularly reviewed to facilitate independent testing.

In addition, the results of the programme provide reassurance that independent testing by the competent authorities can be performed efficiently if there is a need to verify the quality of a medicine on the market.

The results also indicate that the Agency's risk-based approach continues to be a useful and valid tool for the selection of products to be included in surveillance programmes.

The Agency's approach to developing common test procedures for generic medicines allows for a broad and rapid screening of the quality of generic medicinal products that are currently on the EU market.

The effective operation of the sampling and testing programme is the result of ongoing close collaboration between the Agency, the EDQM, the national competent authorities and the network of the OMCLs. This collaboration leads to the continuous improvement of the programme.

7. Annexes

Annex 1: List of products tested in the 2014 programme[4]

	Product	Pharmaceutical form	Human / Veterinary
1	Actraphane / Mixtard	Suspension for injection	Hum
2	Apidra	Solution for injection	Hum
3	Avonex	Solution for injection	Hum
4	BeneFIX	Powder and solvent for solution for injection	Hum
5	Caelyx	Concentrate for solution for infusion	Hum
6	Competact	Film-coated tablet	Hum
7	Crixivan	Capsule, hard	Hum
8	Dynastat	Powder and solvent for solution for injection	Hum
9	Entacapone Teva	Film-coated tablet	Hum
10	Gliolan	Powder for oral solution	Hum
11	Glustin	Tablet	Hum
12	Incivo	Film-coated tablet	Hum
13	Insulatard/Protaphane	Suspension for injection	Hum
14	Jevtana	Concentrate and solvent for solution for infusion	Hum
15	Kogenate Bayer / Helixate NexGen	Powder and solvent for solution for injection	Hum
16	Levemir	Solution for injection	Hum
17	Liprolog	Solution for injection	Hum
18	Liprolog	Suspension for injection	Hum
19	Masivet	Film-coated tablet	Vet
20	Myocet	Powder, dispersion and solvent for concentrate for dispersion for infusion	Hum
21	NovoRapid	Solution for injection	Hum
22	Nulojix	Powder for concentrate for solution for infusion	Hum
23	Palladia	Tablets	Vet
24	Panacur AquaSol	Oral suspension	Vet
25	PecFent	Nasal spray solution	Hum
26	Pirsue	Intramammary solution	Vet

[4] For the purpose of the figures contained in this report, a 'product' can include 2 or more medicinal products (with different marketing authorisation numbers) which are identical

	Product	Pharmaceutical form	Human / Veterinary
27	Poulvac E. coli	Lyophilisate for suspension for spray administration	Vet
28	Profender	Modified-release tablet	Vet
29	Puregon/Fertavid	Solution for injection	Hum
30	Respiporc Flu3	Suspension for injection	Vet
31	Suprelorin	Implant	Vet
32	Thyrogen	Powder for solution for injection	Hum
33	Topotecan Actavis	Powder for concentrate for solution for infusion	Hum
34	Tresiba	Solution for injection in pre-filled pen	Hum
35	Vectibix	Concentrate for solution for infusion	Hum
36	Velcade	Powder for solution for infusion	Hum
37	Xalkori	Capsule, hard	Hum
38	Yervoy	Concentrate for solution for infusion	Hum

Pramipexole Generic programme

	Product	Pharmaceutical form	Human / Veterinary
39	Mirapexin/Sifrol	Tablet	Hum
40	Oprymea	Tablet	Hum
41	Pramipexole Accord	Tablet	Hum
42	Pramipexole Teva	Tablet	Hum

Telmisartan Generic programme

	Product	Pharmaceutical form	Human / Veterinary
43	Kinzalmono/Pritor	Tablet	Hum
44	Micardis	Tablet	Hum
45	Telmisartan Actavis	Tablet	Hum
46	Telmisartan Teva / Telmisartan Teva Pharma	Tablet	Hum
47	Tolura	Tablet	Hum

Annex 2: List of inspectorates participating in the 2014 programme[5]

	Country	National Authority name
1	Austria	Agentur Gesundheit Ernährungssicherheit, AGES
2	Belgium	Agence Federale des Medicaments et Produits de Santé, AFMPS
3	Croatia	Agency for Medicinal Products and Medical Devices, HALMED
4	Cyprus	Ministry of Health
5	Czech Republic	State Institute for Drug Control, SUKL
6		Institute State Control of Veterinary Biologicals, USKVBL
7	Denmark	Danish Health and Medicines Authority, DHMA
8	Estonia	State Agency Medicines, SAM
9	Finland	Finnish Medicines Agency, FIMEA
10	France	Agence Nationale du Médicament Vétérinaire, ANSES
11		Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM
12	Germany	Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten , ZLG
13	Greece	National Organization for Medicines, EOF
14	Hungary	National Institute of Pharmacy, NIP
15		Central Agricultural Office
16	Iceland	Icelandic Medicines Control Agency
17	Ireland	Health Products Regulatory Authority, HPRA
18	Italy	Italian Medicines Agency – AIFA
19	Latvia	Health Inspectorate
20	Lithuania	State Medicines Control Agency
21	Luxembourg	Ministère de la Santé, Division de la Pharmacie et des Médicaments
22	Malta	Medicines Authority
23	The Netherlands	Inspectie voor de Gezondheidszorg
24		Nederlandse Voedsel- en Warenautoritieit, NVWA
25	Norway	Norwegian Medicines Agency, NOMA
26	Portugal	Direcção Geral de Veterinaria
27		Instituto Nacional da Farmacia e do Medicamento , INFARMED
28	Romania	National Agency for Medicines and Medical Devices
29		Institute for control of Biological Products and Veterinary Medicines
30	Spain	Agencia Espanola de Medicamentos Y Productos Sanitarios, AEMPS
31	Slovakia	State Institute for Drug Control
32	Slovenia	Agency for Medicinal Products and Medical Devices, JAZMP
33	Sweden	Medical Products Agency
34	United Kingdom	Medicines And Healthcare Products Regulatory Agency, MHRA

[5] Source: EDQM

Annex 3: List of laboratories participating in the 2014 programme[6]

	Country	Laboratory name and town
1	Austria	AGES-C - AGES MEA (Chemicals & Pharmaceuticals), Vienna
2	Belgium	IPH-C - Scientific Institute of Public Health - Medicines Section, Brussels
3	Bulgaria	BDA - Bulgarian Drug Agency, Sofia
4	Croatia	ALMP - Agency for Medicinal Products and Medical Devices, Zagreb
5	Cyprus	SGL - Laboratory for the Quality Control of Pharmaceuticals, Cosmetics and Food Suppl., Nicosia
6	Czech Republic	SUKL - State Institute for Drug Control, Laboratory Control Section, Prague
7		USKVBL - Institute for State Control of Veterinary Biologicals and Medicaments, Brno
8	Denmark	DHMA - Danish Health and Medicines Authority, Copenhagen
9	Estonia	SAM - State Agency of Medicines, Quality Control Laboratory, Tartu
10	Finland	FIMEA - Finnish Medicines Agency/ Laboratory, Helsinki
11	France	Anses - Laboratoire de Ploufragan
12		ANSM - Direction des Laboratoires et des Contrôles - Site de Montpellier, Vendargues
13		ANSM - Direction des Laboratoires et des Contrôles, Site de Saint-Denis
14	Germany	BW - Chemisches und Veterinäruntersuchungsaamt Karlsruhe, CVUA, Karlsruhe
15		NW - Arzneimitteluntersuchungsstelle NRW, Münster
16		LLBB - Landeslabor Berlin-Brandenburg, Berlin
17		PEI - Paul-Ehrlich Institut, Langen
18	Hungary	DVMP - National Food Chain Safety Office - Directorate of Veterinary Medicinal Products, Budapest
19		NIP - Laboratory of National Institute of Pharmacy, Budapest
20	Ireland	HPRA_PALG - Public Analyst's Laboratory, Galway
21	Italy	ISS-H - Istituto Superiore di Sanità, Roma
22	Latvia	SAM - Medicines Examination Laboratory, Riga
23	Lithuania	VVKT- State Medicines Control Agency / Medicines Control Laboratory, Vilnius
24	Luxembourg	LNS - Laboratoire National de Santé, Service du Contrôle des Médicaments, Luxembourg
25	The Netherlands	RIVM-B - Centre for Health Protection (Biologicals), Bilthoven
26		RIVM-C – Centre for Health Protection (Chemicals), Bilthoven
27	Norway	NOMA - Norwegian Medicines Agency, Oslo
28	Poland	NIL - National Medicines Institute, Warsaw
29	Portugal	INFARMED I.P. - National Authority for Medicines and Health Products, Lisbon
30	Slovenia	JAZMP - Agency for Medicinal Products and Medical Devices, Ljubljana
31	Slovakia	SUKL, State Institute for Drug Control, Bratislava
32	Spain	AEMPS-C - Spanish Agency of Medicines and Medical Devices, Chem. and Pharm. Div., Madrid
33	Sweden	MPA - Medical Products Agency, Uppsala
34	Switzerland	SWISSMEDIC - Division OMCL (laboratory), Swissmedic, Swiss Agency for Therapeutic Products, Bern
35	United Kingdom	NIBSC - National Institute for Biological Standards & Control, Potter's Bar
36		MHRA_LGC - Laboratory of the Government Chemist, Teddington

[6] Source: EDQM