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Inspections and Human Medicines Pharmacovigilance Division

Results of the sampling and testing programme for the year 2013

Human and veterinary products

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Table of contents

Glossary

CAP:	Centrally Authorised Product
CHMP:	Committee for Medicinal Products for Human Use
CVMP:	Committee for Medicinal Products for Veterinary Use
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
NCA:	National Competent Authorities
MAH:	Marketing Authorisation Holder
OMCL:	Official Medicines Control Laboratory
PL:	Package Leaflet
SOP:	Standard Operating Procedure

1. Executive summary

This report describes the results of the 2013 sampling and testing programme coordinated by the European Medicines Agency (hereinafter "the Agency") in accordance with Regulation (EC) 726/2004, Art. 57(r).

A total of 45 centrally authorised products (CAPs) were sampled from the European Economic Area market and tested. This exercise required the cooperation of 34 inspectorates for the sampling and of 35 official laboratories (OMCL) for the testing. Most of the products tested (97%) complied with the authorised specifications. One veterinary product was found to be out of specification and following assessment there was no need to recall the affected batch from the market.

The samplers performed checks of the printed packaging materials on the samples taken in order to verify potential non-compliances with the marketing authorisations. One non-compliance was detected and a quality defect procedure was initiated.

The sampling and testing programme is a valuable tool that allows the Agency to supervise the quality of the centrally authorised products available on the EEA market.

2. Introduction

The Agency co-ordinates the sampling and testing programme each year in accordance with Art. 57 (r) of Regulation (EC) 726/2004 (1). This allows the Agency to verify that the centrally authorised medicinal products on the market comply with their authorised quality specifications. Additionally, this monitoring activity allows the Agency to verify that the analytical methods used by the manufacturers for the control of the products are satisfactory.

The Agency collaborates with other institutional partners (EDQM, OMCL network, national competent authorities, inspection services and rapporteurs), and with the marketing-authorisation holders (MAHs); each of these partners plays an important role in the success of the programmes.

The report provides information on the procedural aspects of the programme 2013 and the test results.

3. The sampling and testing programme 2013

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, and more targeted use of limited resources.

The list was adopted by the CHMP and the CVMP in February 2012. For the list of products tested see Annex 1.

The MAHs were asked to provide the EDQM with the documentation and material necessary to carry out the testing.

The relevant rapporteurs provided advice and recommendations on the parameters to be tested for each product.

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:

Number of products	Number of inspectorates	Number of samples taken
45 (38 Human and 7 Veterinary)	34	119

3.3. Label and package leaflets checks

Checks on labels and package leaflets (PL) were carried out by the samplers using a checklist prepared by the EMA and the EDQM in order to assist in this process.

The purpose of the exercise was not to perform a full label and PL check of compliance, but rather to highlight potential issues for further investigation.

A total of 117 samples were taken from the market (2 samples were provided directly by the MAHs to the testing laboratories), and the labels and PLs were examined.

Labels/PL checked	Followed-up as quality defects
117	1

For 40 labels (out of the 117 examined) there was the need to carry out some additional investigation. One label resulted to be non-compliant and a quality defect procedure was initiated resulting in the company implementing the relevant corrective actions.

3.4. Testing

Testing of the products started in March 2013. Chemical products and insulin products were tested in one laboratory only. When needed, a back-up laboratory was available. Biological and veterinary immunological products were tested in two laboratories.

Below is a table summarising the testing phase:

Number of products tested	Number of Laboratories
45	35

The EDQM prepared and sent test reports to the Agency.

Testing results were classified using a 1–3 scale according to their 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. Results

Below is a table summarising the results:

Product type	Products tested	1 = compliant / no issues identified	2 = compliant but issues of scientific editorial or regulatory nature were identified	3 = non compliant / out of specifications
Human	38	21	17	0
Veterinary	7	3	3	1
Total	**45**	**24**	**20**	**1**

From the 20 products for which issues were identified, only 6 were deemed to be significant and required actions to improve the quality of the documented methodology. For the other 14 products, the clarifications provided by the MAHs were found to be satisfactory and therefore there was no need to implement any action.

No. of Products	Variations	Update SOPs / testing documentation	No regulatory action
Human	2	2	13
Veterinary	1	1	1
Total	3	3	14

5. Discussion

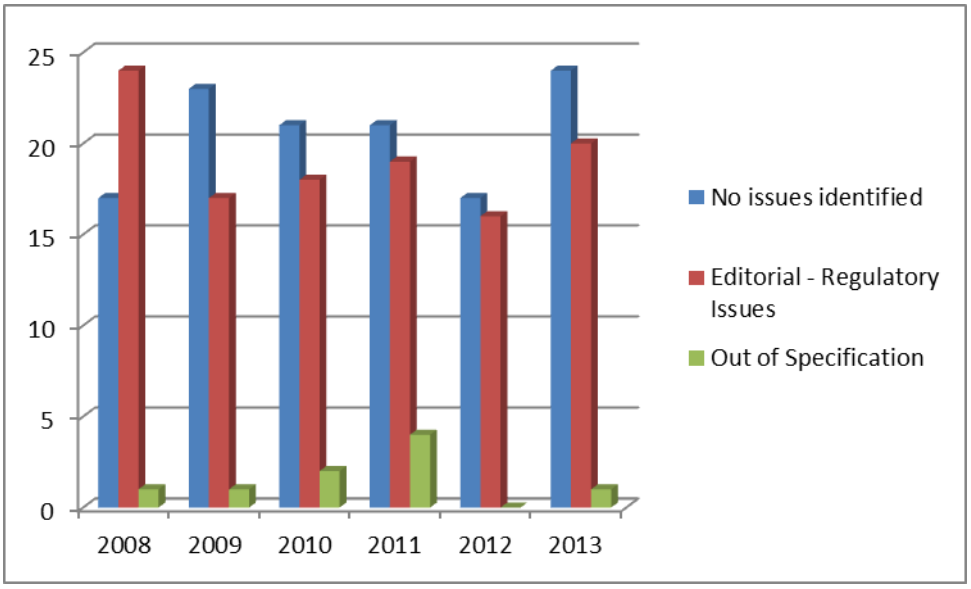
Most of the products tested (44 out of 45) complied with their authorised specifications. Nevertheless, for 20 of these products some issues of technical, scientific, regulatory or editorial nature in relation to the testing methodology were identified, and these were highlighted in the testing reports. In order to address these issues, the Agency had extensive contacts with the relevant rapporteurs and MAHs which contributed to clarify some aspects of the testing methods. However, for 6 products this was not sufficient and eventually the MAHs committed to improve the methods either by amending their internal testing documentation or by submitting a variation.

One veterinary product was reported to be “out of specification” in relation to the content of an excipient. A quality defect procedure was initiated and the out of specification result was assessed by the rapporteurs and the supervisory authority. It was concluded that there were no safety or efficacy concerns for the product, and that no recall of the batch was needed. The MAH proposed corrective actions by improving their testing methods.

Being “out of specification” will affect the ‘risk’ status of the product, as determined by the risk-based approach which drives the selection of centrally authorised products to be included in the sampling and testing programmes. This methodology has been implemented for the selection of products since 2010 (human), and it is based on a series of risk factors that have been identified, and that can be applicable to the various products; each product is given a score which depends on whether each factor does or does not apply to the product itself. Every year, the various centrally authorised products (and their pharmaceutical forms) are scored according to this methodology, which forms the basis for the preparation of the list of products to be included in the sampling and testing programmes.

The results of the 2013 programme broadly reflect those obtained in the previous years, as illustrated in the comparative graph below; this shows that most of the products comply with their authorised specifications, with only a limited number of products resulting to be out-of-specification.

Outcome of sampling & testing since 2008:



However, the outcome of the testing performed by the OMCLs seems to suggest that the description of the testing methods is not always adequate and would benefit from some improvements or clarifications to allow testing to be carried out by an independent laboratory. For this reason, the actions taken by the Agency, the rapporteurs and the MAHs in following-up the testing results represent an important contribution to addressing these shortcomings.

6. Conclusions and recommendations

Most of the products tested in the 2013 programme were in compliance with their authorised specifications, with one veterinary product found to be outside its specifications. A quality defect procedure was initiated and, following the investigation from the company and the assessment of the issue by the rapporteurs and the supervisory authority, the defect procedure was finalised satisfactorily.

The results of the 2013 programme are in line with the results of the previous years’ showing that, at least for the batches sampled, products are consistently of the expected quality.

For about 44% of the products tested (20 out of 45), some issues of technical, scientific, regulatory or editorial nature were identified and reported by the EDQM. This is also in line with the previous years’ results.

The actions taken by the Agency, in cooperation with the rapporteurs and the MAH, to address these issues, represent a contribution to the improvement of the products' documentation and to the accuracy of the test methods.

As such, it can be concluded that the sampling and testing programmes are part of the overall Agency's task of supervision of the medicinal products placed on the market.

7. References

- 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

- Risk-based approach

  http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500005114.pdf

- Sampling and testing website

  http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000174.jsp&mid=WC0b01ac058002708d

8. Annexes

Annex 1: List of products tested in the 2013 programme[1]

	Product	Pharmaceutical form	Human / Veterinary
1	Actos	Tablet	Hum
2	Aerius/Azomyr	Orodispersible tablet	Hum
3	Aerius/Azomyr/Neoclarityn	Oral solution	Hum
4	Aloxi	Soft capsule	Hum
5	Aptivus	Soft capsule	Hum
6	Aptivus	Oral Solution	Hum
7	Aranesp	Solution for injection	Hum
8	Arzerra	Concentrate for solution for infusion	Hum
9	Beromun	Powder and solvent for solution for infusion	Hum
10	Biograstim	Solution for injection or infusion	Hum
11	Cerezyme	Powder for concentrate for solution for infusion	Hum
12	Combivir	Film-coated tablet	Hum
13	Cymbalta/Xeristar	Gastro-resistant capsule, hard	Hum
14	Dicural	Solution for injection	Vet
15	Econor	Premix for medicated feed	Vet
16	Epivir	Oral solution	Hum
17	Ferriprox	Film-coated tablet	Hum
18	Ferriprox	Oral Solution	Hum
19	Glivec	Capsule, hard	Hum
20	Glivec	Film-coated tablet	Hum
21	Hycamtin	Powder for concentrate for solution for infusion	Hum
22	Hycamtin	Hard capsule	Hum
23	Iressa	Film-coated tablet	Hum
24	Locatim	Oral solution	Vet
25	Mabthera	Concentrate for solution for infusion	Hum
26	Metalyse	Powder and solvent for solution for injection	Hum
27	MS-H Vaccine	Eyedrop suspension	Vet
28	Neulasta	Solution for injection	Hum
29	Nobilis IB4-91	A lyophilised vaccine pellet for reconstitution	Vet
30	Novoseven	Powder and solvent for solution for injection	Hum
31	Nutropinaq	Solution for injection	Hum
32	Plenadren	Modified-release tablet	Hum
33	Prac-Tic	Spot-on solution	Vet
34	Procox	Oral suspension	Vet
35	Rapamune	Oral solution	Hum
36	Revasc	Powder and solvent for solution for injection	Hum

[1] 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
37	Simulect	Powder and solvent for solution for injection or infusion	Hum
38	Sonata	Hard capsule	Hum
39	Teysuno	Hard capsule	Hum
40	Trizivir	Film-coated tablet	Hum
41	Vfend	Powder for solution for infusion	Hum
42	Viramune	Oral suspension	Hum
43	Viramune	Prolonged-release tablet	Hum
44	Zerit	Hard capsule	Hum
45	Ziagen	Oral solution	Hum

Annex 2: List of inspectorates participating in the 2013 programme[2]

	Country	National Authority name
1	Austria	AGES PharmMed
2	Belgium	Agence Federale des Medicaments et Produits de Santé, AFMPS
3	Cyprus	Ministry of Health
4	Czech Republic	State Institute for Drug Control
5		Institute State Control of Veterinary Biologicals
6	Denmark	Danish Health and Medicines Authority
7	Estonia	State Agency Medicines
8	Finland	Finnish Medicines Agency, FIMEA
9	France	Agence Nationale du Médicament Vétérinaire, ANSES
10		Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM
11	Germany	Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten , ZLG
12	Greece	National Organization for Medicines
13	Hungary	National Institute of Pharmacy
14	Iceland	Icelandic Medicines Control Agency
15	Ireland	Irish Medicines Board, IMB
16	Italy	Ministerio della Salute – AIFA
17		Ministerio della Sanita
18	Latvia	Health Inspectorate
19	Lithuania	State Medicines Control Agency
20	Luxembourg	Ministère de la Santé, Division de la Pharmacie et des Médicaments
21	The Netherlands	Inspectie voor de Gezondheidszorg
22		Nederlandse Voedsel- en Warenautoritieit, NVWA
23	Norway	Norwegian Medicines Agency, NOMA
24	Poland	Main Pharmaceutical Inspectorate
25	Portugal	Direcção Geral de Veterinaria
26		Instituto Nacional da Farmacia e do Medicamento , INFARMED
27	Romania	National Agency for Medicines and Medical Devices
28		Veterinary Medicines Institute for control of Biological Products and Veterinary
29	Spain	Agencia Espanola de Medicamentos Y Productos Sanitarios, AEMPS
30	Slovakia	State Institute for Drug Control
31		Institute for State Control of Veterinary Biologicals and Medicaments
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

[2] Source: EDQM

Annex 3: List of laboratories participating in the 2013 programme[3]

	Country	Laboratory name and town
1	Austria	AGES-B - AGES MEA (Biologicals), Vienna
2		AGES-C - AGES MEA (Chemicals & Pharmaceuticals), Vienna
3	Belgium	IPH-C - Scientific Institute of Public Health - Medicines Section, Brussels
4	Bulgaria	BDA - Bulgarian Drug Agency, Sofia
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	Germany	AMI - Arzneimitteluntersuchungsinstitut –Nord GmbH, Bremen
8		BW - Chemisches und Veterinäruntersuchungsaamt Karlsruhe, CVUA Karlsruhe
9		BY - Landesamt für Gesundheit und Lebensmittelsicherheit, Oberschleißheim
10		PEI - Paul-Ehrlich Institut, Langen
11	Denmark	DHMA - Danish Health and Medicines Authority (formerly Danish Medicines Authority), Copenhagen
12	Estonia	SAM - State Agency of Medicines, Quality Control Laboratory, Tartu
13	Greece	EOF - Laboratory Division of the National Organization for Medicines, Athens
14	Spain	AEMPS-B - Spanish Agency of Medicines and Medical Devices, Biological and Biotechnological Division, Madrid
15		AEMPS-C - Spanish Agency of Medicines and Medical Devices, Chem. and Pharm. Div., Madrid
16	Finland	FIMEA - Finnish Medicines Agency/ Laboratory, Helsinki
17	France	ANSES - Agence Nationale du Médicament Vétérinaire, Fougères
18		ANSM - Direction des Laboratoires et des Contrôles - Site de Montpellier, Vendargues
19		ANSM - Direction des Laboratoires et des Contrôles, Site de Saint-Denis
20	Hungary	DVMP - National Food Chain Safety Office - Directorate of Veterinary Medicinal Products, Budapest
21		NIP - Laboratory of National Institute of Pharmacy, Budapest
22	Ireland	IMB_HPRA_PALG - Public Analyst's Laboratory, Galway
23	Italy	ISS-H - Istituto Superiore di Sanità, Roma
24	Lithuania	VVKT- State Medicines Control Agency / Medicines Control Laboratory, Vilnius
25	Luxembourg	LNS - Laboratoire National de Santé, Service du Contrôle des Médicaments, Luxembourg
26	Latvia	SAM - Medicines Examination Laboratory, Riga
27	The Netherlands	RIVM-B - Centre for Health Protection (Biologicals), Bilthoven
28	Norway	NOMA - Norwegian Medicines Agency, Oslo
29	Poland	NIL - National Medicines Institute, Warsaw
30	Portugal	INFARMED I.P. - National Authority for Medicines and Health Products, Lisbon
31	Sweden	MPA - Medical Products Agency, Uppsala
32	Slovenia	JAZMP - Agency for Medicinal Products and Medical Devices, Ljubljana
33	Slovak Republic	SUKL - State Institute for Drug Control, Bratislava
34	United Kingdom	MHRA - Laboratory of the Government Chemist, LGC, Teddington
35		NIBSC - National Institute for Biological Standards & Control, Potter's Bar

[3] Source: EDQM