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Compliance and Inspection

Results of the Sampling and Testing programme for the year 2010

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Executive Summary

The present report contains information on the management and the outcomes of the Sampling and Testing Programme for the year 2010. These programmes are organised and co-ordinated every year by the EMA, in order to comply with its legal obligations under Art. 57(r)[1] of Regulation (EC) 726/2004. The main aim of the programmes is to verify that the centrally authorised medicinal products on the market comply with their authorised quality specifications. Additionally, this monitoring activity allows checking that the analytical methods used by the manufacturers for the control of the products are satisfactory.

A list of products to be tested in 2010, established by the EMA Manufacturing and Quality Compliance Section, was adopted by the CHMP and the CVMP at the beginning of 2009. The parameters to be tested were selected on the basis of the Rapporteurs' advice.

The programme was carried out in cooperation with the European Directorate for the Quality of Medicines and HealthCare (EDQM), and with the National Competent Authorities of the EEA Member States.

A total of 42 products were included in the programme.

At the time this report is prepared, testing of one product has yet to be completed, and therefore results for this product will be included in the report on the 2011 Sampling and Testing Programme.

For the first time, upon request from the EMA, checks on the labels and PILs of the products sampled have been carried out. This is a pilot exercise which should contribute to enhance the level of compliance of the CAPs product information.

Below is a table summarising the testing results:

Products Tested	1 = No problems identified	2 = Issues identified	3 = Out of specification	4 = Out of specification (Health risk)
Total = 41	21	18	2	0
Human = 33	19	14	0	0
Veterinary = 8	2	4	2	0

There were 2 'out of specification' results, meaning that the products did not comply with their authorised specifications and were consequently handled in accordance with Community procedures as suspected quality defects. There were no products for which testing showed problems that could represent an immediate concern for patients (health risk).

According to the established procedure, for each product tested a report was issued. The reports were circulated to the relevant MAHs for comments, and to the relevant Rapporteurs with the request to provide suggestions for follow-up actions where appropriate. The issues identified during the testing were followed-up by the Manufacturing and Quality Compliance Section, and they were addressed by the concerned MAHs mainly through amendment of the testing documentation.

[1] Article 57
1. The Agency shall provide the Member States and the institutions of the Community with the best possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human or veterinary use which is referred to it in accordance with the provisions of Community legislation relating to medicinal products. To this end, the Agency, acting particularly through its committees, shall undertake the following tasks:

(r) coordination of 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;

Report

Introduction

Art. 57 (r) of Council Regulation (EC) 726/2004, requires the EMA 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.

As a joint initiative of the European Commission, the European Medicines Agency, the European Directorate for the Quality of Medicines and HealthCare (EDQM) and the network of Official Medicines Control Laboratories in the EEA, a trial Sampling and Testing Programme was organised in 1997-1998 that included a limited number of products only. This was followed, starting with the years 1999/2000, by regular, annual programmes. The one carried out in 2010 was the 11th of such programmes.

In 2007 the EMA started working on the development of a risk-based model for the selection of Centrally Authorised Products to be included in the Sampling and Testing Programmes. The selection of human products for the 2010 programme was made using the risk-based principles developed since that time.

Medicinal products for veterinary use were selected for testing on the basis of the year of their authorisation; according to this criterion, which was normal practice for all products in the previous years' programmes, products are to be tested three years after authorisation.

As usual, samples were taken from the markets of three different Member States, and they were tested by national OMCLs.

The EMA – Manufacturing and Quality Compliance Section - had the responsibility for the overall co-ordination of the Sampling and Testing Programmes.

The present report contains information on the management and the outcomes of the programme carried out in the year 2010 with the exception of one product, whose testing has yet to be completed.

EMA has noted that a significant number of quality defects reported, are caused by errors in the labelling of the product or in the PIL. For this reason checking of labels and PILs was included in the 2010 programme as a trial exercise. The purpose of this additional monitoring activity is to identify relatively obvious potential non-compliances, and to follow them up with the MAHs using the quality defect procedure.

Endorsement of the list of products and preparatory work

Lists of products to be tested were submitted to the CHMP and the CVMP in January 2009, and were endorsed by the relevant Committee. The lists included products to be tested for the first time as well as products already tested in the past. During the preparatory work some products were deleted from the list (mainly because not available on the market or due to supply shortages) and replaced with other medicines. Eventually 41 products were tested and testing of one product is still ongoing.

For the list of products see Annex 2.

Following the established procedure, once the lists were endorsed and finalised the Manufacturing and Quality Compliance Section wrote to the Marketing Authorisation Holders (MAHs) of the products selected. They were informed of the inclusion of their products in the testing programme, and asked to provide the documentation and the material needed to carry out the testing.

The Manufacturing and Quality Compliance Section also wrote to the Rapporteur and CoRapporteur for each product, in order to obtain a recommendation on the testing parameters that they considered would act as indicator of the product's quality.

Sampling

Samples of the products were drawn by inspectors of the competent national authorities, from their respective national markets. The inspectors were provided with vouchers, which were used to obtain samples of medicinal product. The vouchers were later redeemed by the pharmacies/hospitals/wholesalers with equivalent quantities of products supplied by the MAH.

In general each product was sampled in three different Member States.

Parallel distribution of centrally authorised products is, on some national markets, a well established practice. In order to make sure that parallel distributed products are included in this supervision activity, in 2010 the EMA requested product sampling also from the Parallel Distribution chain. However it was not possible to obtain any parallel distributed sample during this programme owing to the often transient nature of the business.

Testing Results

Testing of the products started in March 2010 and it was carried out by the national Official Medicines Control Laboratories (OMCLs). The 2010 Sampling and Testing Programme was the fourth of such programmes in which the "single laboratory testing scheme for chemical products" was fully implemented (all the chemical products were tested in one laboratory only). This approach, which has now become well established, allows a better use of the resources made available by the national authorities, while maintaining an adequate level of supervision. When needed, a back-up laboratory was available.

The same "single laboratory testing" approach was also followed for the testing of the insulin analogues included in the programme.

The EDQM prepared and sent to the EMA, on an on-going basis, CAP Testing Reports (one for each product) containing details of the testing results.

The testing results were classified according to the following 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 (no Health Risk)
4 Out of specification results (Health risk)

Below is a table summarising the testing results:

Products Tested	1 = No problems identified	2 = Issues identified	3 = Out of specification	4 = Out of specification (Health risk)
Total = 41	21	18	2	0
Human = 33	19	14	0	0
Veterinary = 8	2	4	2	0

For 21 of the 41 products tested, no problems were identified and there was no reason to question the quality of the batches tested or the testing methods.

For 18 products, some issues (scientific, regulatory, technical or editorial) were identified.

For 2 products out of specification results were obtained. These were both veterinary products.

There were no products for which testing showed problems that could represent an immediate concern for patients (health risk).

Follow up to the testing

Report circulation

Following a consolidated procedure, the testing reports were first circulated to the Marketing Authorisation Holders, with the request to provide their comments on the testing results.

The comments from the companies, and the reports, were then circulated to the Rapporteurs:

- For the products for which no problems were identified, the reports were sent to the Rapporteur for information only.
- For products for which some issues were identified during the testing, the reports were circulated to the Rapporteurs with the request to provide their advice for follow-up actions. A reply sheet was attached to the correspondence, and a deadline for reply was indicated.
- For the two products for which an 'out of specification' result was detected, as soon as the information was made available to the EMA, the suspected quality defect procedure was initiated in accordance with Community procedures.

Rapporteurs' advice

The Rapporteurs are expected to communicate their advice for follow-up actions, ideally using the reply sheet provided by the Manufacturing and Quality Compliance Section. It is the task of the Section to act on this feedback, which in 2010 was provided on 9 occasions. For those products for which no feedback was provided, it was the understanding of the Section that the Rapporteurs were satisfied with the quality of the batches tested or with the responses and commitments provided by the MAHs, or that the issues highlighted in the testing reports did not require any follow-up.

Outcome

Most of the problems identified during the testing were in relation to the detail of the analytical procedures authorised or used for the control of the medicinal products. In order to address these issues, the Manufacturing and Quality Compliance Section had extensive contacts with the Marketing Authorisation Holders, which resulted, in most of the cases, in the MAH submitting variation applications.

For products reported to be `out of specification`, a Suspected Quality Defect procedure was initiated and further assessment required the MAH to submit a variation. No recall of the batches was initiated for the products.

File closure

The Manufacturing and Quality Compliance Section proceeded to the closure of the testing product files on the basis of the criteria outlined in the document SOP/INSP/2011 (public).

Conclusions

The results of the 2010 programme showed that most of the products tested were in compliance with the authorised specifications. For products reported to be `out of specification`, a Suspected Quality Defect procedure was initiated and further assessment required the MAH to submit a variation. No recall of the batches was initiated for the products.

For about 44% of the marketed products tested (18 out of 41) some issues of technical, scientific, regulatory or editorial nature were identified.

In view of the results obtained in the 2010 Sampling and Testing Programme, it can be concluded that this annual monitoring exercise continues to be an important tool in the implementation of the EMA task of supervision of medicinal products placed on the market.

Annex 1: Acronyms

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
EEA:	European Economic Area, formed by the Members of the European Union and Iceland, Liechtenstein and Norway
OMCL:	Official Medicines Control Laboratory
MAH:	Marketing Authorisation Holder
PIL:	Product Information Leaflet

Annex 2: List of products tested in the 2010 programme

	Product	Pharmaceutical form
1	Actraphane / Mixtard	Suspension for injection
2	Advate	Powder and solvent for solution for injection
3	Altargo	Ointment
4	Apidra	Solution for injection
5	Avaglim	Film coated tablet
6	Avandamet	Film coated tablet
7	Avandia	Film coated tablet
8	Avonex	Solution for injection
9	Azopt	Eye drops suspension
10	Benefix	Powder and solvent for solution for injection
11	Circovac	Emulsion and suspension for emulsion for injection
12	Cortavance	Cutaneous spray, solution
13	Emtriva	Hard capsule
14	Enbrel	Solution for injection
15	Enbrel	Powder and solvent for solution for injection for paediatric use
16	Erbitux	Solution for infusion
17	Exforge	Film coated tablet
18	Humalog	Suspension for injection
19	Humalog	Solution for injection
20	Insulatard/Protaphane	Suspension for injection
21	Insuman Comb 15	Suspension for injection
22	IntronA	Solution for injection or infusion
23	Kaletra	Film coated tablet
24	Kogenate Bayer/Helixate NexGen	Powder and solvent for solution for injection
25	Levemir	Solution for injection
26	Meloxidyl	Oral suspension
27	Meloxivet	Oral suspension
28	Myfenax	Hard capsule
29	NovoRapid	Solution for injection
30	Orencia	Powder for concentrate for solution for infusion
31	PegIntron/ViraferonPeg	Powder and solvent for solution for injection
32	Prilactone	Tablet
33	Rapamune	Coated tablet
34	Remicade	Powder for concentrate for solution for infusion
35	Slentrol	Oral solution
36	Stalevo	Film coated tablet
37	Suprelorin	Implant
38	Vaxxitek HVT + IBD	Frozen suspension and diluent for injection
39	Vectibix	Concentrate for solution for infusion
40	Viramune	Tablet
41	Xolair	Powder and solvent for solution for injection
42	Ypozane	Tablet

Annex 3: List of Inspectorates participating in the 2010 programme

Country	Name
Austria	Ages Pharmmed
Belgium	Agence Federale Des Medicaments Et Produits De Sante
Czech Republic	State Institute For Drug Control Institute State Control Of Veterinary Biologicals
Cyprus	Ministry Of Health, GMP Inspectorate Ministry Of Agriculture, Veterinary Services
Denmark	Danish Medicines Agency
Finland	Finnish Medicines Agency
France	French Health Products Safety Agency National Agency for veterinary medicinal products - French Agency for food, environmental and occupational health safety
Germany	Bezirksregierung Arnsberg Ministerium Fur Gesundheit Und Verbraucherschutz Staatliches Gewerbeaufsichtsamt, Hannover Regierungspraesidium, Darmstadt
Greece	National Organization For Medicines
Hungary	Central Agricultural Office, Directorate Of Veterinary Medicinal Products National Institute Of Pharmacy
Iceland	Icelandic Medicines Control Agency
Ireland	Irish Medicines Board
Italy	Ministero Della Salute
Lithuania	State Medicines Control Agency, Ministry Of Health
Luxembourg	Ministere De La Sante, Division Sante Medicaments
Malta	Malta's Medicines Authority
The Netherlands	General Inspection Service, Healthcare Inspectorate
Norway	Norwegian Medicines Agency
Poland	Main Pharmaceutical Inspectorate
Portugal	Instituto Nacional Da Farmacia E Do Medicamento Direccao De Veterinaria
Romania	National Medicines Agency Institute For Control Of Veterinary Biological Products And Medcines
Spain	Agencia Espanola De Medicamentos Y Productos Sanitarios
Slovak Republic	State Institute For Drug Control
Slovenia	Agency Of Medicinal Products And Medical Devices
Sweden	Medical Products Agency
United Kingdom	Medicines And Healthcare Products Regulatory Agency

Annex 4: List of Laboratories participating in the 2010 programme

Country	Name
Austria	AGES PharmMed (Chemicals & Pharmaceuticals), Vienna
Belgium	Scientific Institute of Public Health - Medicines Section, Brussels
Bulgaria	Bulgarian Drug Agency, Sofia National Veterinary Service, Institute for Control of Veterinary Medicinal Products, Sofia
Cyprus	Laboratory for the Quality Control of Pharmaceuticals, Cosmetics and Food Supplements, Nicosia
Czech Republic	Institute for State Control of Veterinary Biologicals and Medicaments, Brno State Institute for Drug Control, Prague
Denmark	Danish Medicines Agency, Copenhagen
Estonia	State Agency of Medicines, Tartu
Finland	Finnish Medicines Agency/ Laboratory, Helsinki
France	Agence Française de Sécurité Sanitaire des Produits de Santé, Vendargues Agence Française de Sécurité Sanitaire des Produits de Santé, Saint-Denis Agence Nationale du Médicament Vétérinaire, Fougeres
Germany	Paul Ehrlich Institut, Langen Arzneimitteluntersuchungsinstitut –Nord GmbH, Bremen Chemisches und Veterinär-Untersuchungsamt, Karlsruhe
Greece	Laboratory Division of the National Organization for Medicines, Athens
Hungary	Central Agricultural Office - Directorate of Veterinary Medicinal Products
Ireland	Public Analyst's Laboratory, Galway
Italy	Istituto Superiore di Sanità, Roma
Latvia	Medicines Examination Laboratory, Riga
Lithuania	State Medicines Control Agency / Medicines Control Laboratory, Vilnius
Luxembourg	Laboratoire National de Santé, Luxembourg
The Netherlands	Centre for Biological Medicines and Medical Technology, Bilthoven Centre for Quality Control of Chemical-Pharmaceutical Products, Bilthoven
Norway	Norwegian Medicines Agency, Oslo
Poland	National Medicines Institute, Warsaw
Portugal	National Authority for Medicines and Health Products, Lisbon
Romania	Institute for Control of Veterinary Biological Products and Medicines, Bucharest
Slovenia	Agency for Medicinal Products and Medical Devices, Ljubljana
Sweden	Medical Product Agency, Uppsala
Spain	Spanish Agency of Medicines and Medical Devices, Madrid
United Kingdom	National Institute for Biological Standards & Control, Teddington