EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 February 2010
EMA/INS/S&T/34689/2010
Compliance and Inspection

Results of the Sampling and Testing Programme for the year 2008

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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 2008. These Programmes are organised and co-ordinated every year by the European Medicines Agency, in order to comply with its legal obligations under Art. 57 (r) of Regulation (EC) 726/2004[1]. 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 to 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 2008, established by the Agency's Inspections Sector, was endorsed by the CHMP and the CVMP at the beginning of 2007. 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.

For the purpose of the assessment of a type II variation, in March 2008 the CHMP asked the Inspections Sector to organise, within the framework of the 2008 Programme, the testing of ReFacto - in addition to the testing of the same product already planned. Further to this CHMP request, the total number of products tested raised to 42.

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 = 42	17	24	1	0
Human = 36 (*)	15	20 (*)	1	0
Veterinary = 6	2	4	0	0

(*)These numbers include testing of ReFacto, for the purpose of the assessment of a Type II variation.

There was 1 'out of specification' result, meaning that the product didn't comply with its authorised quality characteristics. 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. The issues identified during the testing were followed-up by the Inspections Sector, 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 Agency 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 (OMCL) 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, in 1997-1998 a trial phase was initiated, which included a limited number of products. This was followed, starting with the years 1999/2000, by regular, annual programmes. The one carried out in 2008 was the 9th such programme.

At the time of the 2008 programme, as in previous years, products were selected for testing on the basis of the year of their authorisation; in general products were tested three years after authorisation. Additionally some products already tested in the past could be included for the purpose of re-testing.

Samples are taken from the markets of three different Member States, and they are tested by national OMCLs.

The European Medicines Agency – Inspections Sector has 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 2008.

• Endorsement of the list of products and preparatory work

Lists of products to be tested were submitted to the CHMP and the CVMP in February 2007, and they were endorsed by the two Committees. The lists included products to be tested for the first time, and products already tested in the past but for which re-testing could be envisaged. Eventually the Agency's Secretariat prepared a list of 41 products (35 Human medicinal products and 6 Veterinary medicinal products) to be included in the annual programme. This was in line with the number of products tested in previous Programmes (around 40 products).

On the basis of a request from the CHMP, in March 2008 the Human medicinal product ReFacto was added to the list of products to be tested, bringing the total to 42 (36 Human and 6 Veterinary medicinal products). For the complete list of products see Annex 2.

Following a well-established procedure, once the list was endorsed and finalised the Inspections Sector 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 they were asked to provide the documentation and the materials needed to carry out the testing.

The Inspections Sector also wrote to the Rapporteur and CoRapporteur for each product, in order to obtain a recommendation on the testing parameters that they considered would best act as indicators 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 countries. There was no sampling for Sonata (the testing was a follow-up to the 2006 Programme, and it was carried out on the samples taken in 2006) or for the ReFacto ad-hoc testing (samples were provided directly by the MAH).

• Testing Results

Testing of the products started in March 2008 and it was carried out by the national Official Medicines Control Laboratories (OMCLs). The 2008 Sampling and Testing Programme was the second programme in which the "single laboratory testing scheme for chemical products" was fully implemented (chemical products were tested in one laboratory only). This approach allows a better use of the resources made available by the national authorities, whilst ensuring an adequate level of supervision. When needed, a back-up laboratory was available.

The EDQM prepared and sent to the Agency, on an on-going basis, CAP Testing Reports (one for each product) containing details of the testing results. Results for the two couples of identical products Corlentor/Procoralan, and Helixate NexGen/Kogenate Bayer were reported together.

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 (potential 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 = 42	17	24	1	0
Human = 36 (*)	15	20 (*)	1	0
Veterinary = 6	2	4	0	0

(*)These numbers include testing of ReFacto, for the purpose of the assessment of a Type II variation

For 17 of the 42 products tested, no problems were identified and there was no reason to question the quality of the batches tested or the testing methods.

For 24 products, some issues (scientific, regulatory, technical or editorial) were identified.

There was 1 product for which 'out of specification' results were detected.

Finally, as in the previous years, there were no products for which testing showed problems that could represent an immediate concern for patients (health risk)

• Follow up to the testing

– Reports circulation

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

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

- For the products reports in which no problems were identified, these were sent to the Rapporteur for information only.

- For those products for which some issues were identified during the testing, the reports were circulated to the Rapporteurs requesting their advice for follow-up actions. A reply sheet was attached to the correspondence, and a deadline for the reply was indicated.

- For the only product for which an 'out of specification' result was detected, as soon as the confirmed information was made available to the Agency, 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 Inspections Sector; it is then the role of the Inspections Sector to act on this feedback. For those products for which no feedback was provided, it was the understanding of the Inspections Sector 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 didn't 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 product. In order to address these issues, the Inspections Sector had extensive contacts with the Marketing Authorisation Holders which resulted, in some cases, in the MAH submitting variation applications.

  For the product reported to be 'out of specifications', further investigation and assessment showed that the problem didn't represent a health risk for the patients.

- **File closure**

  The Inspections Sector 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 2008 Programme showed that most of the products tested were in compliance with the authorised specifications. For the only product for which 'out of specifications' results were detected, the investigation and the assessment that followed concluded that they didn't represent a health risk for the patients. There were no instances of quality defects raising immediate concern for public or animal health.

For about 57% of the marketed products tested some issues of technical, scientific, regulatory or editorial nature were identified. The relevant reports were circulated to the Rapporteurs, with the request to provide suggestions for possible follow-up actions. These resulted, in most of the cases, in the MAH amending parts of the testing documentation.

In view of the results obtained in the 2008 Sampling and Testing Programme, it can be concluded that this annual monitoring exercise continues to be an important tool in the implementation of the European Medicines Agency 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

OMCL = Official Medicines Control Laboratory

MAH = Marketing Authorisation Holder

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

Annex 2: List of Products tested

	Product	Pharmaceutical form
1	Aloxi	solution for injection
2	Aptivus	soft capsules
3	Avastin	concentrate for solution for infusion
4	Azilect	tablets
5	Betaferon	powder and solvent for solution for injection
6	Cholestagel	film coated tablets
7	Corlentor	film coated tablets
8	Dynepo	solution for injection
9	Equilis Prequenza Te (veterinary)	suspension for injection
10	Fosavance	tablets
11	Helicobacter Test INFAI	powder for oral solution
12	Helixate NexGen	powder and solvent for solution for injection
13	Humalog	solution for injection
14	Hycamtin	powder for concentrate for solution for infusion
15	Insuman	suspension for injection
16	Invirase	hard capsules
17	Kepivance	powder for solution for injection
18	KOGENATE Bayer	powder and solvent for solution for injection
19	Metacam (veterinary)	oral suspension
20	Naxcel (veterinary)	suspension for injection
21	Nobilis OR Inac (veterinary)	emulsion for injection
22	Novorapid	solution for injection
23	NovoSeven	powder and solvent for solution for injection
24	Noxafil	oral suspension
25	Orfadin	hard capsules
26	Osigraft	powder for suspension for implantation
27	Prialt	solution for infusion
28	Procoralan	film coated tablets
29	Profender (veterinary)	spot-on solution
30	Purevax RCPCh FeLV (veterinary)	powder (lyophilisate) and solvent for suspension for injection
31	Rapilysin	powder and solvent for solution for injection
32	Rebetol	oral solution
33	ReFacto	powder and solvent for solution for injection
34	ReFacto (ad hoc testing)	powder and solvent for solution for injection
35	Sonata	hard capsules
36	Tarceva	film coated tablets
37	Truvada	film coated tablets
38	Vasovist	solution for injection
39	Xolair	powder and solvent for solution for injection
40	Xyrem	oral solution
41	Zerit	hard capsules
42	Zonegran	hard capsules

Annex 3: List of Inspectorates participating in the 2008 Programme[2]

COUNTRY	NAME
Austria	Agentur für Gesundheit und Ernährungssicherheit GmbH (AGES PharmMed)
Belgium	Agence Fédérale des Médicaments et des Produits de Santé
Bulgaria	Bulgarian Drug Agency
Czech Republic	State Institute for Drug Control Institute for State Control of Veterinary Biologicals and Medicaments
Cyprus	Ministry of Health – Pharmaceutical Service Veterinary Services
Denmark	Danish Medicines Agency
Estonia	State Agency of Medicines
Finland	National Agency for Medicines
France	Agence Française de Sécurité Sanitaire des Produits de Santé
Germany	Bezirksregierung Münster Bezirksregierung Arnsberg Regierung von Oberbayern Regierungspräsidium Tübingen Bezirksregierung Düsseldorf
Greece	National Organization for Medicines
Hungary	National Institute of Pharmacy Central Agricultural Office Directorate for Veterinary Medicinal Products
Iceland	Icelandic Medicines Control Agency
Ireland	Irish Medicines Board
Italy	Agenzia Italiana del Farmaco Ministero della Salute
Latvia	Health Inspectorate
Lithuania	State Medicines Control Agency
Luxembourg	Division de la Pharmacie et des Médicaments – Direction de la Santé
The Netherlands	Healthcare Inspectorate
Norway	Norwegian Medicines Agency
Poland	Glowny Inspektorat Farmaceutyczny (Main Pharmaceutical Inspectorates)
Portugal	Instituto Nacional da Farmacia e do Medicamento (INFARMED) Direcçao general de veterinaria Autoridade Nacional do Medicamento e Produtos de Saúde, I.P
Romania	National Medicines Agency
Spain	Agencia Espanola de Medicamentos y Productos Sanitarios
Slovak Republic	State Institute for Drug Control USKVBL
Slovenia	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia
Sweden	Medical Products Agency
United-Kingdom	Medicines and Healthcare Products Regulatory Agency

[2] Source: EDQM

Annex 4: List of Laboratories participating in the 2008 Programme[3]

COUNTRY	NAME
Austria	Österreichische Agentur für Gesundheit und Ernährungssicherheit PharmMed – Vienna
Belgium	Scientific Institute for Public Health, Brussels Veterinary and agrochemical research center (CODA-CERVA-VAR), Ukkel
Bulgaria	Department for analysis of medicinal products – Bulgarian Drug Agency, Sofia
Cyprus	Laboratory for Quality Control of the Pharmaceuticals and Cosmetics – State General Laboratory – 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 of Estonia, Tartu
Finland	National Agency for Medicines, Helsinki
France	Agence Française de Sécurité Sanitaire des Produits de Santé, Saint-Denis Agence Française de Sécurité Sanitaire des Produits de Santé, Montpellier-Vendargues
Germany	Arzneimitteluntersuchungsinstitut-Nord, Bremen Chemisches und Veterinäruntersuchungsamt, Karlsruhe Landesinstitut für Gesundheit und Arbeit des Landes Nordrhein-Westfalen, Münster Paul Ehrlich Institut, Langen Berliner Betrieb für Gesundheitliche Aufgaben, Berlin
Greece	National Drug Organization, Holargos
Hungary	National Institute of Pharmacy, Budapest Central Agricultural Office directorate for Veterinary Products, Budapest
Ireland	Public Analyst's Laboratory, Galway
Italy	Instituto Superiore di Sanità, Rome
Latvia	State Agency of Medicines, Riga
Lithuania	State Medicines Control Agency, Vilnius
Luxembourg	Laboratoire National de Santé, Luxembourg
The Netherlands	National Institute for Public Health and the Environment – Bilthoven Central Veterinary Institute (CVI), Lelystadt
Norway	Norwegian Medicines Agency, Oslo
Poland	National Medicines Institute, Warsaw
Portugal	IFARMED, Lisbon National Authority of Medicines and Health Products, IP, Lisbon
Romania	National Medicines Agency – Bucharest
Slovenia	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia
Sweden	Medical Product Agency, Uppsala
United-Kingdom	MHRA at LGC Laboratory, Teddington National Institute for Biological Standards & Control (NIBSC), Hertfordshire

[3] Source: EDQM