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Compliance and Inspection

Results of the Sampling and Testing Programme for the year 2009

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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 2009. 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 2009, established by the EMA Manufacturing and Quality Compliance Section, was adopted by the CHMP and the CVMP at the beginning of 2008. 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 was included in the Programme. For the first time, a sample of a product taken from the parallel distribution chain was also tested.

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	23	17	1	1
Human = 34	18	16	0	0
Veterinary = 8	5	1	1	1

There were 2 'out of specification' results, meaning that the products did not comply with their authorised specifications. These were both veterinary products. Out of these two, there was 1 product for which testing showed problems that could represent an immediate concern for the animals.

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, in 1997-1998 a trial Sampling and Testing Programme was organised, which 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 2009 was the 10th 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 2009 Programme was made using some of the risk-based principles under development at 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 2009.

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 2008, 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), and replaced with other medicines. Eventually 42 products were tested.

For the complete 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. The standard sampling practice could not be carried out for three products and these were sampled in one Member State only.

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 2009 the EMA requested product sampling also from the Parallel Distribution chain. Eventually only one parallel distributed sample was obtained, which was found to be in compliance.

Testing Results

Testing of the products started in February 2009 and it was carried out by the national Official Medicines Control Laboratories (OMCLs). The 2009 Sampling and Testing Programme was the third 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 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 = 42	23	17	1	1
Human = 34	18	16	0	0
Veterinary = 8	5	1	1	1

For 23 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 17 products, some issues (scientific, regulatory, technical or editorial) were identified.

There were 2 products for which 'out of specification' results were detected. These were both veterinary products. Out of these two, there was 1 product for which testing showed problems that could represent an immediate concern for the animals.

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. 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 one of the products reported to be `out of specification`, a Suspected Quality Defect procedure was initiated and further assessment required the MAH to submit a variation.

For the other product also a Suspected Quality Defect report was issued, and a batch recall organised as a precautionary measure; this was followed by a suspension of the marketing authorisation by the CVMP, until appropriate resolution of the issues by the MAH.

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 2009 Programme showed that most of the products tested were in compliance with the authorised specifications. For one of the products that was found to be 'out of specification' a Suspected Quality Defect procedure was initiated, and after assessment the MAH was asked to submit a variation to update the shelf-life specifications for the product.

The other product that was found to be 'out of specification' raised immediate concern for animal health. A Suspected Quality Defect and recall of all the batches were initiated, which were followed by the suspension of the marketing authorisation until satisfactory resolution of the issues by the MAH.

For about 40% of the marketed products tested (17 out of 42) 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.

In view of the results obtained in the 2009 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

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

EMA = European Medicines Agency

Annex 2: List of Products tested

	Product	Pharmaceutical form
1	Aivlosin	oral powder
2	ATryn	powder for solution for infusion
3	Avonex	powder and solvent for solution for injection
4	Baraclude	film coated tablets
5	Baraclude	oral solution
6	Byetta	solution for injection
7	Caelyx	concentrate for solution for infusion
8	Cerenia	Tablets
9	Cerenia	solution for injection
10	Champix	film coated tablets
11	Competact	film coated tablets
12	Convenia	powder and solvent for solution for injection
13	Cubicin	powder for concentrate for solution for infusion
14	DuoTrav	eye drops solution
15	Evoltra	concentrate for solution for infusion
16	Flexicam	oral suspension
17	Ganfort	eye drops solution
18	Herceptin	powder for concentrate for solution for infusion
19	Insuman	solution for injection
20	Intrinsa / Livensa	transdermal patch
21	Lantus	solution for injection
22	Macugen	solution for injection
23	Medicinal Oxigen Air Liquide Sante	inhalation gas
24	Myozyme	powder for concentrate for solution for infusion
25	Naglazyme	concentrate for solution for infusion
26	Neorecormon	powder and solvent for solution for injection
27	Neupro	transdermal patch
28	Novomix	suspension for injection
29	Omnitrope	powder and solvent for solution for injection
30	Omnitrope	solution for injection in a cartridge
31	Preotact	powder and solvent for solution for injection
32	ProteqFlu Te	suspension for injection
33	Puregon	solution for injection
34	Savene	powder for concentrate and diluent for solution for infusion
35	Siklos	film coated tablets
36	Sprycel	film coated tablets
37	Sutent	hard capsules
38	Thelin	film coated tablets
39	Tygacil	solution for injection
40	Tysabri	concentrate for solution for infusion
41	Yarvitan	oral solution
42	Yttriga	radiopharmaceutical precursor, solution

Annex 3: List of Inspectorates participating in the 2009 Programme

COUNTRY	NAME
Austria	Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH
Belgium	Agence Fédérale des Médicaments et des Produits de Santé
Bulgaria	Националната ветеринарномедицинска служба
Czech Republic	Státní ústav pro kontrolu léčiv Ústav pro státní kontrolu veterinárních biopreparátů a léčiv
Cyprus	Υπουργείο Υγείας
Denmark	Lægemiddelstyrelsen
Estonia	Ravimiamet
Finland	Lääkealan turvallisuus- ja kehittämiskeskus Fimea
France	Agence Française de Sécurité Sanitaire des Produits de Santé
Germany	Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten Bezirksregierung Detmold Regierung von Unterfranken Regierung von Oberbayern Regierungspräsidium Tübingen
Greece	Εθνικός Οργανισμός Φαρμάκων
Hungary	Országos Gyógyszerészeti Intézet Mezőgazdasági Szakigazgatási Hivatal Központ, Állatgyógyászati Termékek Igazgatósága
Iceland	Lyfjastofnun
Ireland	Irish Medicines Board
Italy	Agenzia Italiana del Farmaco
Lithuania	Valstybinė vaistų kontrolės tarnyba
Luxembourg	Division de la Pharmacie et des Médicaments – Direction de la Santé
Malta	Awtorità dwar il-Mediċini
The Netherlands	Inspectie voor de Gezondheidszorg
Norway	Statens Legemiddelverk
Poland	Glowny Inspektorat Farmaceutyczny
Portugal	Instituto Nacional da Farmacia e do Medicamento Direcçao general de veterinaria Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.
Romania	Agenţia Naţională a Medicamentului
Spain	Agencia Espanola de Medicamentos y Productos Sanitarios
Slovak Republic	Štátny ústav pre kontrolu liečiv
Slovenia	Javna agencija Republike Slovenije za zdravila in medicinske pripomočke
Sweden	Läkemedelsverket
United Kingdom	Medicines and Healthcare Products Regulatory Agency

Annex 4: List of Laboratories participating in the 2009 Programme

COUNTRY	NAME
Austria	Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH, Vienna
Belgium	Institut Scientifique de Santé Publique, Brussels
Bulgaria	Изпълнителна агенция по лекарствата, Sofia
Cyprus	State General Laboratory, Nicosia
Czech Republic	Institute for State Control of Veterinary Biologicals and Medicaments, Brno Státní ústav pro kontrolu léčiv
Denmark	Lægemiddelstyrelsen, Copenhagen
Estonia	Ravimiamet, Tartu
Finland	Lääkealan turvallisuus- ja kehittämiskeskus Fimea, Helsinki
France	Agence Française de Sécurité Sanitaire des Produits de Santé, Saint-Denis Agence Française de Sécurité Sanitaire des Produits de Santé, Montpellier Agence Nationale du Médicament Vétérinaire - Agence Française de Sécurité Sanitaire des Aliments, Fougères Cedex
Germany	Chemisches und Veterinäruntersuchungsamt, Karlsruhe Paul Ehrlich Institut, Langen Zentrales Institut des Sanitätsdienstes der Bundeswehr, München
Greece	Εθνικός Οργανισμός Φαρμάκων, Holargos
Hungary	Országos Gyógyszerészeti Intézet, Budapest Mezőgazdasági Szakigazgatási Hivatal Központ, Állatgyógyászati Termékek Igazgatósága, Budapest
Ireland	Public Analyst's Laboratory, Galway
Italy	Instituto Superiore di Sanità, Rome
Latvia	Zāļu valsts aģentūra, Riga
Lithuania	Valstybinė vaistų kontrolės tarnyba, Vilnius
Luxembourg	Laboratoire National de Santé, Luxembourg
The Netherlands	Rijksinstituut voor Volksgezondheid en Milieu, Bilthoven
Norway	Statens Legemiddelverk, Oslo
Poland	Narodowy Instytut Leków, Warsaw
Portugal	Autoridade Nacional do Medicamento e Produtos de Saúde, I.P, Lisbon
Romania	Agenţia Naţională a Medicamentului, Bucharest
Spain	Agencia Espanola de Medicamentos y Productos Sanitarios, Madrid
Sweden	Läkemedelsverket, Uppsala
United Kingdom	Medicines Healthcare Products Regulatory Agency, London National Institute for Biological Standards and Control, South Mimms