2008

Annual Report

Medicines Authority

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2008 Highlights

- Capacity building for Malta to work as Reference Member State in the European procedures through a Twinning project, staff development and further recruitment
- Evaluation on Reference Member State dossier started
- The setting up of the Medicines Review Committee
- First Collective Agreement between the UĦM and the Medicines Authority
- Update in the procedure for Performance Monitoring
- Improved staff relations at all levels
- First Inspection of the National Blood Establishment
- More active involvement in the EU working parties and committees

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1.0 Introduction

1.1 Overview of the Main Objectives and Achievements

The main objectives of the Medicines Authority for 2008 was for Malta to start participating in the Decentralised Procedure as Reference Member State (RMS). In order to reach this objective the Authority needed to train its staff as well as continue building its human resource capacity. The Authority took part in a Twinning project with The Netherlands and this was a successful experience, with great benefits in terms of capacity building and a generated positive attitude for RMS assessment and work in general. The process for Performance Monitoring was prioritized and the measures for monitoring of performance were updated. The Collective Agreement between the UHM and the Medicines Authority was finalised and signed in February 2008. During 2008 a planned programme for improving relations with and between staff at all levels was held with the help of an external expert. The organisation encountered a number of hurdles in terms of recruitment as the process is lengthy and requires numerous steps and also because of lack of availability of appropriate candidates to fill the posts. The delays in capacity building affected the business of the Medicines Authority. While the Authority started full assessment of its first RMS dossier, it was not possible start new procedures as RMS in the Decentralised procedure as the required resources for the work were not available. Nevertheless, the Authority successfully conducted its first inspection of the National Blood Establishment. The support of the Irish Medicines Board for this inspection proved to be a good model for undertaking novel areas of inspection.

1.2 Management Cycle

Eleven (11) management meetings were held during 2008. Management meetings covered management decisions, administrative and corporate issues, evaluation of ongoing operations and regulatory aspects. Actions and assignments from previous management meetings were reviewed and reported back to members. Outstanding issues were noted and subsequent action planned and taken accordingly.

The mid-year Management Review has become an integral part of the Medicine's Authority corporate calendar. The Management Review was conducted in September 2008 and covered all departments, personnel and processes. During this meeting, management reviewed the progress achieved during quarter one to three and set targets for the following period (Quarter 4, 2008 and 2009) so as to enhance the status

and effectiveness of the organisation's quality management system. Relevant data was kept during the interim between Management Review 2007 and Management Review 2008. This data was analysed and filtered to present the period's results and performance. Objectives were reviewed and revised in view of results achieved. Corrective action and improvement was recommended where objectives were not met.

2.0 Quality Management

2.1 The Quality Management System

Continual Improvement, development, implementation and maintenance were the key objectives behind the annual year 2008 for the quality management system while keeping in focus customer satisfaction.

The Quality Management System (QMS) at the Medicines Authority is adapted to the ISO 9001:2000 requirements to suit its needs as a regulatory entity, principally in training, in the system of evaluation, and writing of procedures. The mission statement of the Authority and its objectives were discussed at management meetings in light of adopting a new management model and organizational restructuring for the year 2009 as Malta is now participating more actively in the European network as Reference Member State in the Decentralised Procedure. This change has effected and will affect the quality management system. During 2008 the change from processing national applications only to RMS assessment work created a paradigm shift. The self assessment benchmarking exercise known as BEMA II has also effected operations from mid 2008.

The principle objectives of the Quality Manager throughout 2008 were:

- Culture change toward continuous improvement of the QMS
- Development, maintenance and control all documentation in relation to the Medicines Authority's QMS
- Development, introduction and maintenance of systems for monitoring the quality system
- Implementation of quality management roles as specified in quality SOPs in such areas as internal audit, quality improvement, management review, complaints and corrective and preventive action
- Planning and facilitation for the provision of a program of training in the quality management system for all staff

QMS studies took place throughout the year between the CEO and the Quality Manager, followed up by interviews with personnel leading to the revision of existing documentation within the Authority and the introduction of monitoring systems and knowledge systems. The need to involve everyone within the organization to grow with the change in the quality system initiated the start of internal formal meetings within the technical departments. The quality system covers all areas of management, including resources, financial management, environment health and safety, communication, controls, development and training.

During the Management Review for the year 2007 – 2008, the management team lead by the CEO verified the extent to which the system fulfilled ISO 9001:2000 requirement. Further support to maintain, implement planning, monitoring and the need of enforcement were identified. As a result restructuring and the plan for 2009 are drawn up for the areas and sub-areas governed by technical and non technical activities. The Medicines Authority will move ahead to the implementation of an integral QMS in 2009 reflecting the basic principal of continuous improvement while ensuring that the business activities are operating in a controlled manner and the people responsible for the various activities know and understand their roles and responsibilities.

The outcome of the meetings that took place between the CEO and the Quality Manager were also presented at the work group for Quality Managers on 21/05/2008 - 22/05/2008 held in Ireland and on 24th November 2008 through a presentation in Paris. One aspect that was taken up by the other NCA was the induction training on QMS introduced by the Medicines Authority for the new recruits.

The ISO 9001:2000 based QMS is being publicised on the intranet, via email and through meetings with the different individuals within directorates and units. Throughout 2008, much work has been done to improve the intranet and the accessibility of documents electronically. Prior to uploading of documentation on to the intranet, a paper system was in place which was cumbersome and documentation was not being controlled to the satisfaction of the Quality Manager. Hard copy controlled departmental SOPs were being used and misplaced. The Medicines Authority wishes to move towards becoming more fully automated even with regards to process mapping which were introduced in the final quarter of 2008.

The scope of the Quality Manager is to have a knowledge based system which is centralized and controlled through which all levels within the Authority would benefit. The information and knowledge

will enhance personal excellence on the work place. This also adds to the element of transparency towards the staff.

The task is long and continuous as there are currently 74 SOPs in hard copy that are being uploaded on to the link library. Besides procedures, reports of meetings from duty travel, meetings of internal meetings and training material (Twinning Capacity Building) to mention a few other items that have been uploaded for access for all employees.

In 2008 induction training on QMS covering its documents and implementation and management processes, continual improvement, technical statistics and internal quality audits as well as benchmarking was initiated with the first intake of new employees. The program is set in three parts and covers QMS as described above, the Quality Manual and General Quality SOPs. This training has been held twice this year, once in the first quarter of 2008 and the other the in 4th quarter 2008. The Quality Manager worked on a refresher program on QMS for the staff.

Forty two Standard Operating Procedures (SOPs) (most now in their 3rd and 4th revision) were written, approved and are being used to cover all aspects of the Inspectorate activities including Inspection procedures, Enforcement, Sampling, Batch defects and Rapid Alerts handling, Issue of Licences, Clinical Trials and Active Pharmaceutical Ingredients (API's). Aide memoirs are available to assist in the planning of inspections for GMP, GDP, packaging and importation. As part of the Quality System the IED also has an established Memorandum of Understanding (MoU) with Public Health for prosecution services, which is now due for renewal, plus contract agreements for analysis services with Belgian and MHRA OMCL network labs, the latter covering also both sterile and non-sterile dosage forms.

All reports and licenses have been updated and are in the EU format. All Manufacturing Authorizations and GMP certificates have been entered in the Eudra GMP database. Sampling plans for 2005, 2006, and 2007 and now for 2008 have been drawn up and all have been affected. Sampling plan for 2009 has also been drafted.

Quality system improvements were finalized in line with the internal and Canadian audits of 2006 findings. The Quality system is currently also being revised in line with the outcomes of the 2008 internal audits (refer to section 2.3 below).

2.2 EU Benchmarking of European Medicines Agencies (BEMA)

Three benchmarking sessions presented by the Quality Manager to the CEO and the management team were held during the months of July and August. The self assessment questionnaire that had been filled in at the end of December 2007 was also discussed during the sessions as the exercise demanded more interface and communication between directorates and units and individuals as well as demonstration through documentation of managerial decisions and actions to improve the quality system.

The training sessions were conducted through presentations by the BEMA II Steering Group in which BEMA II assessors and Quality Managers also participated to make the DVD into an instruction tool. The emphasis during the sessions was the aim of the benchmarking exercise between the European Medicines Agencies. The aim of the EU/EEA benchmarking system is to contribute to the development of a world class medicines regulatory system for medicinal products based on a network of agencies operating to best practice standards.

The annual self assessment has been carried out in December 2008. Findings and gaps identified during this exercise will be discussed by the CEO and the management team and necessary action taken prior to the BEMA II external benchmarking targeted for week starting 23rd November 2009 when Malta will be assessed by its peers represented by Norway, Netherlands and Germany.

2.3 Internal Audit

The Quality Manager introduced a new system of trainee auditors. This was due to a number of certified auditors having left the authority or were on long leave. It was identified that to implement and manage audit activities in all areas there was a need of a balance of internal auditors to avoid conflict of interest and over stretching the audit team pool. Therefore this lead to the nomination of six members of staff,

technical and non-technical as trainees in our Internal Audit program 2008. This was not well received by the professionally trained auditors, although it was received quite well by the trainees. The internal audit program carried out during 2008 had teams of three one of which was a trainee.

An oral evaluation form has been drawn up and the teams give their feedback together directly to the Quality Manager. So far it seems that the system is working to the benefit of the Authority.

The Internal Audit program was published in March 2008 and this was not well received either. The atmosphere was such that there was resistance leading to delays to the actually start of the internal audits. There were 5 internal audits held during 2008. The areas of activity covered where:

- Quality Defects – Rapid recalls;
- Surveillance programs on marketed drugs including sampling and audit procedure;
- Pharmacovigilance activities;
- Enforcement activities;
- Complaints Procedure for internal and external customers.

The following were specifically targeted:

- Documented decision-making process by individuals, teams and team members. and line managers;
- Documented interface between directorates and units i.e. Inspectorate with Pharmacovigilance and/or assessors or Inspectorate with Administration Unit etc.;
- Documented communication channels between departmental members, line manager and other directorates and units;
- Quality assurance and control.

The reports, corrective and preventive actions proposed have been evaluated by the Quality Manager and the CEO and recommendations submitted during the Management Review 2008, as well as during formal documented meetings such as performance appraisals and staff meetings as well as management meetings. All feedback will be reflected in the overall outcome for implementation plan 2009 and the forthcoming benchmarking exercise in November 2009.

During 2008 the IED had three internal audits carried out for some of its activities, namely; Market Surveillance, Quality Defects and Enforcement procedures. The Directorate is currently in the process of addressing the findings coming out from these internal audits. Some corrective actions have already been made whilst others will be carried forward in first quarter of 2009. In turn the IED also gave its contribution to the Medicines Authority internal audits and have carried out and concluded two audits, one for the post licensing department on its pharmacovigilance activity and the other for the pre-licensing department procedures.

The second internal audit for the Post-Licensing Directorate was conducted in July. All the issues raised are being addressed and feedback given to the CEO regarding the timeframes for rectification. Major issues identified by auditors have been noted and corrective measures are being introduced.

3.0 Human Resouces

3.1 Collective Agreement

During 2008 the Medicines Authority signed and started implementing its first Collective Agreement with the Union Ħaddiema Magħqudin. The collective agreement includes family friendly measures and is part of a restructuring process that the organisation is undertaking.

3.2 Recruitment

The organisation continued with the recruitment process. Three Finance and Administration executives, one Finance and Administration Assistant, one Pre-Clinical Assessor, one Medical Assessor, one Senior Pharmacist and two Pharmacists were recruited externally. There were also internal promotions for the posts of two Senior Pharmacists. In spite of attempts to recruit, the posts of Finance and Administration Manager, Operations and Regulatory Affairs Manager and some posts for Pharmacists and Medical Assessors remained vacant.

In 2008, two assessors (June and August) and two case managers (February and April) resigned from the Medicines Authority. Two Finance and Administration executives joined the Medicines Authority in September 2007 and April 2008. The assessors have not yet been replaced. During 2008, three pharmacists from the Medicines Authority have filled the new posts of senior pharmacists. The additional post of senior pharmacist has been filled by a pharmacist previously employed outside the Medicines Authority. Two pharmacists have also been recruited to replace the vacancies created by recruitment of the three senior pharmacists from internal staff. One pharmacist post is still vacant.

3.3 Staff Development

3.3.1 Team Building

During 2008 a planned programme for improving relations with and between staff at all level was held with the help of an external expert. The programme included increasing communication and trust within the management team, improving relations between management and other members of the staff and also between different directorates. So as to create a better working climate, social activities were regularly organised both inhouse and outside the Authority's premises.

3.3.2 The Twinning 'Light' Project: Further Capacity Building at the Medicines Authority

During 2008, a twining light project between consortium partners The Netherlands Ministry of Health, Welfare and Sport's National Institute for Public Health and the Environment (RIVM) and the Netherlands's Medicines Evaluation Board (MEB) with the Medicines Authority. The project was started in January and was closed in August, thus lasting for eight months. The project aimed at training personnel to carry out work in the areas of licensing, post-licensing and inspection. The activities involved were assessment of EU type dossiers. The training particularly focused on eight sections: Quality module of the dossier (drug substance and drug product), pharmacokinetics of single and prolonged dosage forms, assessment of clinical trial applications, assessment of Herbal and homeopathic products, assessment of the quality dossier of medicinal products (chemicals and biologicals), assessment of blood events (training was given on blood adverse events, risk assessment and assigning imputability levels) and study visits for inspectorate on GxP.

As part of the light twinning project held with the Netherlands, four medicines inspectors participated in three observed inspections in The Hague, consisting of two visits in non sterile solid and liquid dosage forms manufacturing facilities and one visit as an observed GCP inspection.

3.3.3 Training in Malta

During 2008, members of staff of the Medicines Authority received training in the following three areas, pharmacokinetics, pharmaceutics and analytical chemistry.

The four medicines inspectors and the IED director were able to participate also in the working party on QRM held in and organised by the Medicines Authority as part of their new PIC/S membership.

Members of staff attended courses organised by OPM Staff Development Organisation (SDO). Three members of management also started to attend the CAPD sessions for Level II organised by the Health Division training centre. Inhouse training was organised for updated Standard Operating Procedures and on Regulatory issues.

3.3.4 Training abroad

Opportunities for training outside Malta were provided to staff and these cover a whole spectrum of activities of the Authority. Three members of staff of the Post-Licensing Directorate attended four different training sessions abroad. Three training sessions were hosted by the European Medicines Agency and focused on the use of EVDAS software, the assessment of Periodic Safety Update Reports and assessment of Paediatric Investigation Plans. One training session was hosted by the French national competent authority and focused on pharmacokinetics.

The inspectors received training in a number of areas: One medicines inspector attended one session on Quality Risk Management (QRM) principles organised by the PIC/S expert circle on QRM in London, UK. Further training was provided on GCP inspections (special reference to bioequivalence inspections) to two medicines inspectors. There was also another training camp for clinical practice inspectors

provided during September 2008 by EMEA in Barcelona which was attended by one medicines inspector. Moreover, thanks to the good collaboration established with the Irish Medicines Board (IMB), two medicines inspectors attended training in the form of observed inspections carried out at two blood establishments in Ireland. The Inspectorate and Enforcement director also attended in May one training seminar organized by PIC/S and held in Poland on wholesale dealing distribution practices.

4.0 Information Systems Management

During 2008 the IS Department continued to operate and maintain the existing in-house and European information systems and the ICT infrastructure.

Management is considering two models, for the ICT system for licensing of medicinal products namely MDIS in conjunction with EiY or the MEB ICI system to fulfil all licensing requirements. A report was drawn up by the IS Manager which compares the features and costs of the two models.

In February an application was submitted for EU Funds through the ERDF programme. A meeting was held at the PPCD to further discuss the requirements and a set of clarifications was sent to the Authority. Unfortunately the request for funds was not approved.

In February a delegation consisting of the CEO, Pre-Licensing Director and the IS Manager visited the Medicines Evaluation Board (MEB) in the Netherlands for a presentation of their licensing information system known as ICI. The system was custom developed by Accenture and it includes a portal which allows companies to submit applications fully electronically employing the eCTD standard, a comprehensive database with the facility of transmitting medicinal product information to EudraPharm, and a workflow module to help case managers manage procedures more efficiently. In October the IT Manager of the MEB and an Accenture consultant visited the Medicines Authority to deliver a presentation to the management and staff.

Major changes and enhancements were carried out on the LinkLibrary intranet in collaboration with the Quality Manager. The intranet now provides more information, and links are easier to follow.

The improvement on the server setup continued with the benefit of streamlining operations and maximising uptime. Moreover scheduled maintenance is being carried out after office hours.

The Dakar payroll system was extended by implementing a Time and Attendance system to operate the main door and to record timings. The system was set up in such a manner to implement the conditions stipulated in the collective agreement.

5.0 Communication with Stakeholders

Several meetings with individual representatives of companies (manufacturers, local wholesale dealers and marketing authorisation holders) were held in 2008 when these were requested. Meetings with stakeholder groups as required were also held.

The Authority regularly communicated with stakeholders through circulars and these were uploaded on the website so as to assure transparency. The website was updated with relevant information and continuous update of the list of Authorised Medicinal Products (together with SPC and PIL) and the list of licensed wholesale dealers was done. Moreover, the Authority communicated safety and quality issues of medicinal products through circulars.

During 2008, the authority continued its collaboration with University of Tor Vergata (Rome) for the Masters course in Medicines Regulation.

6.0 Participation at Meetings at an EU level

The Medicines Authority is actively involved in a number of EU committees and working parties. The CEO participated at the meetings of the Head of Medicines Agencies and also participated as a member of the EMEA Management Board. The Quality Manager participated at two meetings of the newly formed Working Party of Quality Managers and at two meetings in preparation for BEMA II.

Meetings and working parties attended regularly by staff include the Clinical Trial Facilitation Group (CTFG), the Committee for Medicinal Products for Human Use, the Pharmacovigilance Working Party the Paediatric Committee, and the *ad hoc* group for the development of implementing guidelines for Directive 2001/20/EC.

Other meetings attended include the Coordination Group for the Decentralised and Mutual Recognition Procedures (CMDh), Quality Review of Documents (QRD), HMPC (Committee for Herbal Medicinal Products, HMPWG (Homeopathic Medicinal Product Working Group), Pharmaceutical Committee and the European Medicines Agencies Cooperation on Legal Issues (EMACOLEX)

At the level of the European Commission members of staff of the Medicines Authority participated at the meetings of the Working Party on Pharmaceuticals and Medical Devices and the Standing Committee.

7.0 Internal Technical Committees of the Medicines Authority

7.1 Medicines Review Committee

The Medicines Review Committee (MRC) was set up in July 2008 and seven meetings were held by December 2008. The main aim of the MRC is to carry out any discussions that enhance the process of reaching an integrated opinion on the applications (assessment issues) and for resolving divergences of opinion between reviewers and assessors for all types of licensing procedures. It is also a forum for sharing of information on meetings held at a European level (e.g. CMDh and PhVWP). The MRC members include primarily technical staff from the Pre-licensing and Post-Licensing Directorates. Other members of staff or external experts can also attend if the subject matter or assessments being discussed involve external members. Assessments, in particular where Malta is Reference Member State are discussed in the MRC and a decision on the position to be taken by Malta taken by consensus, following discussion on the issues raised by the assessors. Other assessment and technical issues may also be brought up especially where the assessor/reviewer is of the opinion that a discussion needs to take place for a decision to be taken (e.g. where Malta is Concerned Member State and the position for Malta has to be given) or that the issue may be of interest for the other members, who would benefit from the expertise

or experience of the other members. The experience so far has been positive, although some fine tuning following the experience gained was felt necessary to improve the functioning of this committee. It is planned to consolidate decisions in a scientific/regulatory database in 2009.

7.2 Inspection Review Group

The Inspection Review Group (IRG) ten meetings were held during 2008 whereby twelve cases were discussed and decided upon.

7.3 Borderline Classification Committee

Three (3) meetings of the Borderline Classification Committee were held in 2008. Twenty two (22) products were submitted to the BCC for classification in 2008. The information on the website regarding products classified as medicinal products and the reasons for decisions taken in this regard will be improved thus enabling companies to obtain more information on these decisions and relate it to any of their products that might fall within the 'borderline' category. It is planned that a sub-group of the Borderline Classification Committee, with additional expertise on herbal medicinal products will work extensively on the implementation of the THMP directive.

8.0 Update of Legislation

Following an official negative reply from the European Commission on the request made by Malta for derogation on the implementation of the new data exclusivity periods outlined in Directive 2004/27/EC amending Directive 2001/83/EC, the Medicines (Marketing Authorisation) Regulations of 2007 were amended to update the local legislation in line with the Directives. Therefore, the data exclusivity period for products authorised after October 2005 is now in line with European requirements of eight plus two plus one years as for all other Member States.

During the first quarter of 2008, a Legal Notice entitled "Medicinal Products (Injunction to Advertising) Regulations, 2008" has been published. This legislation continues to transpose Directive 2004/27/EC. Furthermore, the authority was involved during the drafting process of guidelines on advertising concerning medicines, treatments, health claims, nutrition and dietary supplements issued by the broadcasting authority, under the Broadcasting Act, Cap.350.

During 2008 the Inspectorate and Enforcement Department started to implement Legal Notice (LN) 279/2007 (Pharmacy Licence Regulations) published in November 2007, and reviewed all pending applications and started the administrative process to issue the new licences which could be issued in line with the new regulations.

In January 2008 LN 279/2007 was amended via LN 81/2008, whilst two new legal notices were issued: LN 236 / 2008 Pharmacy Licences (Fees) Regulations and LN235 / 2008 Dispensing of Medicinal Products (Foundation for Social Welfare Services) Rules, 2008.

9.0 Licensing of Medicinal Products

9.1 Preparations for Licensing of Medicinal Products with Malta as Reference Member State

The Medicines Authority started to receive several requests to act as Reference Member State, in particular in the Decentralised Procedure. For this reason, a pre-booking form was prepared and made available on the Medicines Authority website, once the decision was taken by the Medicines Authority that Malta will start to process this type of application. The type of applications that will be processed by the Medicines Authority with Malta as Reference Member State are abridged dossiers for oral solid dosage forms, for which training has been provided. Intensive training during the Twinning Light Project in the first two quarters of 2008 prepared the technical staff to assess applications as Reference Member State for these products.

To date ninety five products (95) have been refused as they were not in accordance with the current criteria for acceptance. Thirty two (32) products are eligible and a plan for 2009 is being prepared. With

the current available resources (and the intensive training that covered a period of 6 months and limited the time available for actual processing of applications) no more applications could be accepted.

Malta received the first applications as Reference Member State in December 2007, officially started the first procedure in February 2008 and the second in November 2008.

9.1.1 European Procedures - Mutual Recognition (MRP) and Decentralised Procedures (DCP) Applications with Malta as Concerned Member State (CMS)

During 2008, Malta continued to receive applications with Malta as Concerned Member State. As expected, most applications received were in the Decentralised Procedure as most applicants now prefer this type of procedure for placing a new product on the market. During 2008, for the Mutual Recognition procedure fifty two (52) applications were received and ten (10) marketing authorisations were issued while for the Decentralised Procedure, Malta was included in two hundred and fourteen (214) procedures and eighteen (18) marketing authorisations were issued. From European statistics on these procedures issued by the Coordination Group for Mutual Recognition and Decentralised Procedures (CMDh), it is apparent that Malta, as some other smaller Member States is included in very few procedures when compared to the other Member States. This data is still not made public but it is planned that CMDh will make these statistics public, in view of ongoing discussions on availability and accessibility of medicines for all European citizens.

During 2008, a decision was taken, based on the resources available in the pre-licensing directorate, to enhance the streamlining of processes where Malta is acting as Concerned Member State in the Mutual Recognition or Decentralised procedures Based on a risk-based approach, dossiers for these applications are only assessed in depth in very few situations. The final decision whether to grant or not a marketing authorisation is taken on the basis of the assessment report written by the Reference Member State (in the spirit of true mutual recognition).. These situations have been decided by management and comments sent by Malta are discussed and/or adopted in the Medicines Review Committee. This has allowed for better use of resources in the pre-licensing directorate (which have been mainly deployed for the DCP applications where Malta is Reference Member State) and streamlining of procedures also in other areas. Enhanced efficiency and effectiveness are expected.

The total number of products with a marketing authorisation (national and European procedures) as at end 2008 was one thousand and eighty nine (1989) medicinal products.

Variations

Variation applications were received in 2008 in the MRP and DCP, bringing the total of applications to one thousand six hundred twenty two (1622). One thousand three hundred fifty three (1353) procedures have been finalised.

Renewals

Seventy three (73) MRP and DCP renewal applications have been received in 2008 bringing the cumulative total to one hundred and thirty (130). None have been finalised yet.

Notifications in accordance with article 61(3)

A total of nineteen (19) article 61(3) notifications in the MRP and DCP have been received, fourteen (14) in 2008. One procedure has been finalised.

9.1.2 Authorisations in Accordance with Regulation 4(2) of the Medicines (Marketing Authorisation) Regulations (Article 126a of Directive 2001/83/EC, as Amended)

The Medicines Authority continued to receive applications in accordance with regulation 4(2) of the Medicines (Marketing Authorisation) Regulations (implementing article 126a of Directive 2001/83/EC as amended by Directive 2004/27/EC) during 2008. Data on the applications processed to date is as follows:

In total, nine hundred and fifteen applications (915) have been received to date. In the period 2006 - 2008, seven hundred and fifty one (751) authorisations have been issued (453 in 2008) and seventy nine (79) are pending documentation from the applicants and 8 have been withdrawn by the authorisation holders themselves. Forty (40) applications were refused because they were not eligible for an authorisation. In

total one hundred and forty two (142) authorisation holders hold authorisations in accordance with article 126a. It is difficult to establish a trend for the number of applications that are to be received in 2009. Since December 2006, when the process was initiated, 5 applications were received in that same year, five hundred and seventy four (574) were received in 2007 and three hundred thirty six (336) were received in 2008.

Some complaints were received by the Medicines Authority on the implementation of article 126a applications by Malta. The implementation had been discussed and finalised following extensive consultation with the main stakeholders. Following discussions with the complainants and an explanation of the system for authorisation of these products and the availability issues for Malta, no further action has been taken by any of the complainants, who have in some instances, themselves availed of this system for registration of their products.

9.1.3 Parallel Import Applications

To date one hundred (100) parallel import licence applications have been received. Ninety six (96) licences have been issued. The number of applications for parallel import licences has remained constant in the last three years. Twenty three (23) variations to parallel import licences have been received to date and are in process.

9.1.4 Traditional Herbal Medicinal Products and Homeopathic Products

The implementation of the processes for the authorisation of traditional herbal medicinal products (in accordance with the Herbal Medicinal Products Regulations, 2005) and the authorisation of homeopathic medicinal products is a major project for the Pre-Licensing Directorate in 2009. Liaison with other departments, both within and outside the Ministry for Social Policy will be necessary to start the registration of herbal and homeopathic products currently still being marketed as food supplements but which now should fall under medicines regulation. Following this, a list of all products containing herbal preparations will be compiled. Those requiring registrations will be identified and applications for marketing authorisations will be requested and assessment started accordingly. The same system will be

used for homeopathic preparations that fall under medicines regulations (Chapter 2 of Directive 2001/83/EC as amended).

9.2 National Licensing Activities

9.2.1 National Marketing Authorisations

By the end of 2008, almost all PMA-MA applications have been processed. The applications left pending following the end of the derogation period (end December 2006) were due to missing documentation that was still pending from applicants. Only two pending applications remain. The applicant is awaiting documents from the marketing authorisation holder (MAH) in the source country to be able to finalise.

Status of the PMA-MA Process

Following this process, one thousand six hundred fifty one (1651) marketing authorisations were issued. Thirty two (32) marketing authorisations have been withdrawn by the holders in the meantime. One marketing authorisation has been temporarily suspended for safety reasons until new data is received from the company (product also suspended in the other Member States).

Line Extensions of Nationally Authorised Products / national Applications

To date fifty four (54) line extensions for nationally authorised products have been received in 2008. Forty (40) have been processed. One national application for a locally manufactured product has been received in 2008 and is in process. This brings the total of purely national applications to three.

Variations

By the end of October 2008, a total of two thousand nine hundred and seven (2907) variations were entered into the database. To date, a total of one thousand three hundred and sixty three (1363) variations have been processed. This amounts to 47% of the number of variation applications (all types) received. An improvement in the output has been achieved since the decision was taken to process variations in bulk per product for variations already approved in the country of source. The cooperation of the marketing authorisation holders is being requested to facilitate this process, as frequently the required

information and updated product information is not forthcoming and therefore, it is not always possible to finalise these procedures.

Notifications in accordance with article 61(3)

To date one hundred and eighty six (186) notification applications have been received, one hundred and fifty one (151) in 2008. Forty four (44) have been finalised.

Transfers

One hundred twenty eight (128) marketing authorisation holder transfer applications were received in 2008. A total of two hundred seventy five (275) have been received to date.

Renewals

Twenty (20) national renewals have been received so far. One has been finalised and the rest are being processed.

Withdrawals

By the end of 2008, thirty seven applications for the withdrawal of a marketing authorisation have been received. During this year, a form for the application of a withdrawal of marketing authorisation/licence was created and placed on the website. In this way the withdrawal has been formalized and the reasons for withdrawal are discussed, where applicable, with the marketing authorisation holder, in particular where the product to be withdrawn is considered essential for the local market. A list of withdrawn products is available on the website for reference.

9.3 Linguistic Checks of Dossiers for Centrally Authorised Procedures

The linguistic check process for the product information of centrally authorised products authorised by the European Commission in 2008 were carried out according to the established timelines. Statistics per

type of procedure were as follows: New Products (50), Line Extensions (25), Variations (363), Renewals (38), Referrals (24), Annual Re-assessment (15), Notifications 31/3 (5), Herbal List Entries (5), Urgent Safety Restrictions (1).

10.0 Clinical Trials

Five new Clinical Trials applications were submitted to the Medicines Authority in 2008. Two in total were approved but three were still undergoing assessment as of December 2008. Seventeen (17) amendments to trials which are being conducted in Malta were also received. Thirteen (13) amendments were approved in total in 2008; four amendments are currently still being assessed as of December 2008. All information has been inputted in the European Database for Clinical Trials.

11.0 Pediatric Regulation

The Medicines Authority is actively involved in the implementation of the Pediatric Regulation. During 2008, Medicines Authority representatives at the Paediatric Committee at the European Agency in London were involved as rapporteurs or peer reviewers for fourteen (14) different products (nineteen (19) procedures). As at end 2008, eight of these procedures were concluded, ten (10) were ongoing and one was suspended.

12.0 Pharmacovigilance

The Medicines Authority endeavours in a number of activities to ensure medicinal product safety on the Maltese market and within hospitals. The collection, investigation and reporting of drug safety information in accordance with European requirements comprises one such major pharmacovigilance activity carried out by the Authority. The Medicines Authority may also request modifications to be implemented to medicinal product information following safety signal detection by foreign authorities, the European Medicines Agency (EMEA) and/or international health organisations such as the World Health Organisation (WHO). Safety information updates as supplied by the medicinal products' Marketing Authorisation Holders (MAHs) are also assessed and followed up on a local level. These may sometimes also result in the implementation of product safety recalls in an effort to ensure public safety.

Lastly but not least, the Authority assesses and monitors risk management programmes as proposed by MAHs or as recommended on a European-wide level. The Medicines Authority utilises a number of European information technology application systems and networks for the implementation of the above-mentioned activities.

Reports detailing occurrence of adverse drug reactions to medicinal products available on the market or at hospital are regularly submitted to the Medicines Authority for review and assessment. Such adverse drug reaction reports are mainly compiled and reported by healthcare professionals or the local MAH representatives for the medicinal product concerned. A total of one hundred fifty five (155) adverse drug reaction case reports were registered over 2008. Each of these cases detailed at least one adverse drug reaction to the medicinal product concerned thus resulting in a total of six hundred thirty four (634) individual adverse drug reactions. Figure 1, below gives a breakdown of these adverse drug reactions according to system organ classification. Each case report was assessed by the MA and reported electronically to the EMEA and WHO as the central adverse drug reaction repositories. Adverse drug reaction databases maintained at these organisations typically comprise essential medicinal product safety monitoring tools which allow for the identification of potential/novel safety signals associated with the use of specific drugs particularly when these are administered at certain doses and/or to distinct patient categories.

Figures 2 and 3 further classify the adverse drug reaction case reports (as received over 2008) according to seriousness and patient age respectively. The severity of the adverse drug reaction reports is normally assigned by the reporting healthcare professional or by the Medicines Authority following careful assessment and consideration of applicable factors such as dose of the medicinal product, indication for use, concurrently administered drugs and underlying patient disease.

In 2008, the establishment of a viable electronic reporting system with the EMEA and the WHO comprised a major pharmacovigilance endeavour necessary for the maintenance and reporting of adverse drug reactions according to European legislative requirements. Electronic reporting systems, particularly the use of the EudraVigilance network, were validated and populated with a number of adverse drug reaction reports submitted to the MA over the previous years. Over 2008, in fact, a number of adverse reaction reports as submitted over the years 2006 and 2007 were electronically registered, assessed and subsequently reported to the EMEA and the WHO.

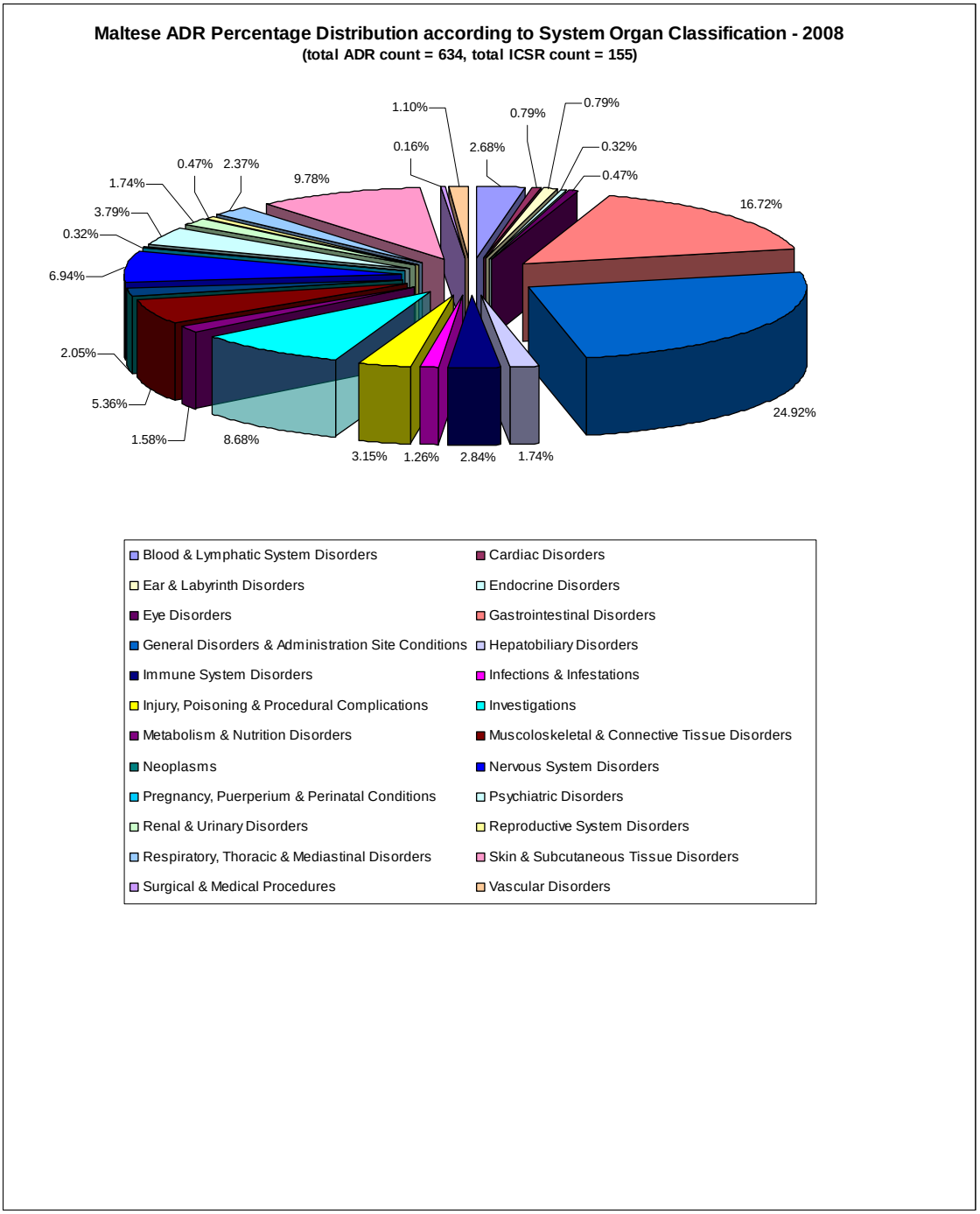

Figure 1: Distribution of adverse drug reactions according to System Organ Classification – 2008

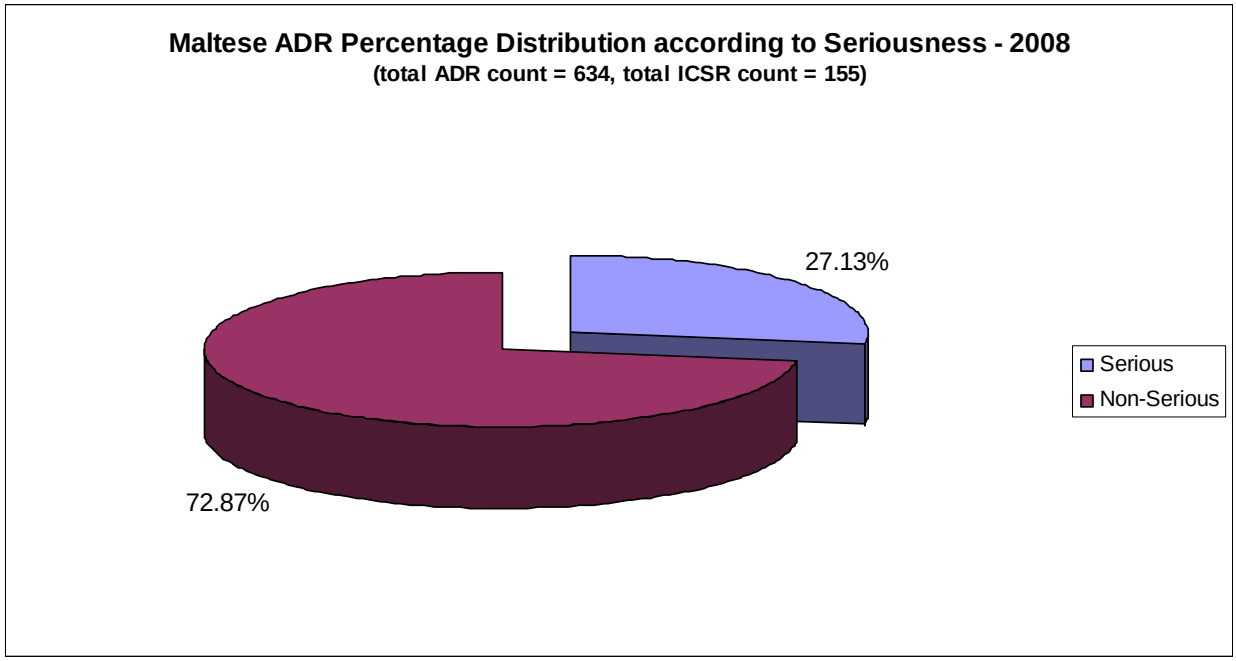

Figure 2: Percentage distribution of adverse drug reactions according to seriousness - 2008

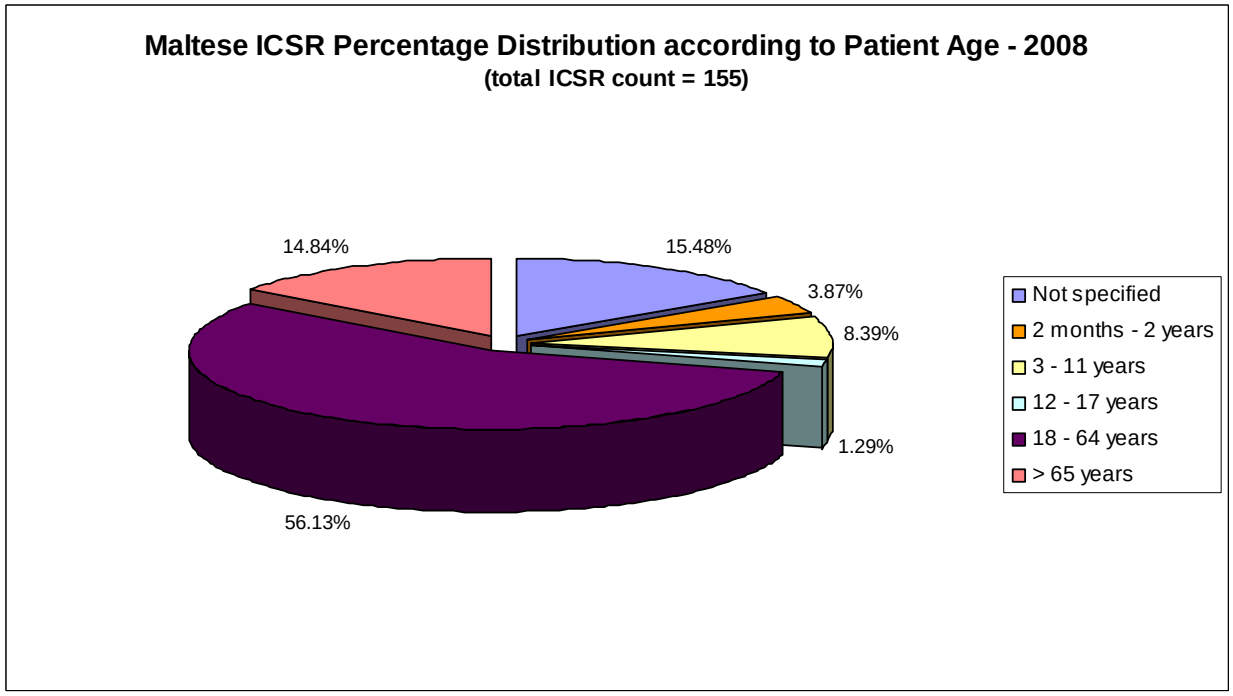

Figure 3: Percentage distribution of case safety reports according to patient age - 2008

Figure 4 below gives the distribution of queries and communications which the Pharmacovigilance Division handled over 2008 in respect of the previously mentioned safety monitoring measures together with those relating to the collection, assessment and reporting of local adverse drug reactions by healthcare professionals and MAH representatives. The latter communications are denoted by the abbreviations: ADRs/SUSARs/PSURs/EudraVigilance.

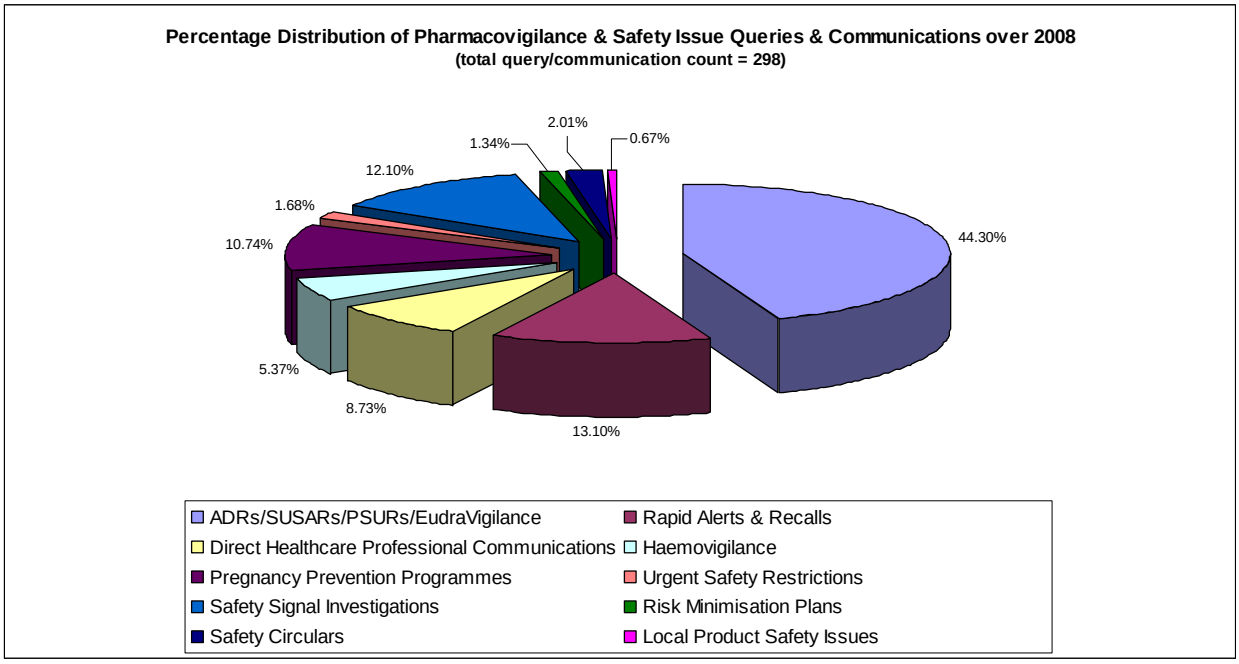

Figure 4: Distribution of pharmacovigilance and safety issue queries and communications - 2008

13.0 Inspection and Licensing of Pharmaceutical Activities

The Inspectorate and Enforcement Directorate (IED) is responsible for inspecting and recommending issuance of licences for manufacturers and wholesale dealers according to national legislation and EU GMP and EU GDP respectively, whilst pharmacies are inspected against national legislation and standards.

13.1 Manufacturing and Importation Authorisations

During 2008 the IED fulfilled its GMP inspection plan where 13 GMP inspections were carried out and concluded as follows:

- Four Manufacturing Authorisations (MAs) were renewed for non sterile solid dose manufacturers;
- One Manufacturing Authorisation (MA) renewed for a medicinal gas manufacturer;
- Four renewals of MAs for repackaging and re-labelling;
- One MA renewed and another new MA issued for importation activity (from outside the EU). Importation is currently from countries which have Mutual Recognition Agreements (MRAs) with the EU for GMP;
- A GMP inspection was also carried out and a GMP certificate issued for the first time to a control laboratory carrying out microbiological testing for the local industry.

An inspection was also carried out in 2008 for the first time ever to the National Blood Establishment against EU directives and standards for blood collection, storage, processing and distribution.

13.2 Authorisations for Wholesale Dealing

During 2008 the IED has also fulfilled its GDP inspection plan where twenty seven (27) GDP inspections were carried out of which two were for new GDP licences.

13.3 Pharmacies

The Directorate took over the responsibility for pharmacies from Public Health in August 2005. During 2008 the Inspectorate and Enforcement Department did not cover the entire inspection plan for pharmacies. From a total of two hundred and eight (208) pharmacies, sixty four (64) were inspected for renewal of their licences. The remaining pharmacy inspections will be carried over to 2009. Another five inspections were carried out in relation to new licences and twelve (12) inspections following variation

applications for pharmacy premises transfers or alterations. Twelve variations for pharmacy licences related to change in licence holder were processed.

One pharmacy licence has been revoked in 2008 because the pharmacy remained closed for more than six months. One new dispensary licence was issued solely for dispensing of medicinal gases directly to patients.

In last quarter of 2007 Inspectorate and Enforcement the Directorate had gone through all the pending pharmacy license applications (349) to ascertain which of these could be processed in line with the new criteria established by the Pharmacy License Regulations brought in force through Legal Notice 279 of 2007. Nineteen (19) applications have been identified which could be processed. In the first half of 2008 these applicants were contacted and the processes initiated to get all the requirements according to legislation prior to an inspection upon which a pharmacy licence can be issued. This process is still ongoing.

A new set of dispensary/pharmacy licence conditions have been drafted and agreed upon with the Licensing Authority which will be issued with next round of pharmacy licences after the consultation period with the involved stakeholders is over.

13.4 Recognition of Qualified Persons

In 2008 the IED received eleven (11) applications for the Qualified Person (QP) status. One applicant did not fulfil the Directive criteria to be considered for the QP status. Seven applicants from the valid ten together with another two who had applied in 2007 were interviewed in three separate interviewing sessions and accepted as being eligible to act as Qualified Persons.

14.0 Enforcement and Surveillance of the Local Market

14.1 Enforcement

Contacts with Customs and Police have been strengthened. The Inspectorate and Enforcement Director attended a meeting in Cyprus in November 2008 on counterfeit products organised by Council of Europe and EDQM, for which representatives of the police force and customs from all the EU member states attended. This is envisaged to continue strengthen the ties which the Inspectorate and Enforcement Department is slowly building with our local colleagues in the Police Force and Customs Department.

During 2008 the directorate carried out twenty (20) enforcement investigations compared to ten (10) in the precedent year, a 100 % increase in enforcement activity. In 2008 the Inspectorate and Enforcement Department changed its approach in enforcement activity for confirmed cases of serious breach of law, where administrative penalties are now being applied according to Legal Notice 264 / 2006, Special Procedure (Penalties in the Respect of the Medicines Act) Regulations 2006. There were four such cases during 2008, one of which the offender paid the incurred administrative penalty whilst the other two were arraigned in court since such penalties were not paid in the prescribed time frame. The other case is still under process.

The Inspectorate and Enforcement Department Director was the group leader for a work-stream within the HMA/WGEO, whereby differences between member states in WDL/Enforcement legislation and inspection/enforcement procedures are being studied.

The Director attended five court sittings during 2008 to provide witness services. Four cases concerned pharmacy issues and one was an enforcement case. Cases related to pharmacy issues are on the increase and a number of cases are pending court jurisdiction.

14.2 Batch Defect Reports

During 2008 the Directorate received eighty six (86) rapid alerts which were investigated and out of which six resulted in a recall from the local market.

14.3 Sampling of Medicinal Products from the Local Market

All results from the sampling plan of 2007 have been received and there were no out of specification results. The sampling plan for 2008 was accomplished, i.e. all fifteen samples were collected and sent for analysis. During 2008 two analyses were carried out in connection with the course of a wholesale dealing inspection which can possibly lead to an enforcement action depending on results received, whilst another analysis was carried out following a patient complaint with concerns over a counterfeit possibility which however have resulted in the negative.

15.0 Regulation of Advertising and Promotional Material

The Medicines Authority monitors the advertising of medicinal products and the issue of any promotional material related to such products and as being presented either to the public or to healthcare professionals.

Monitoring is mainly implemented via the application (in accordance with European legislation) of a self-regulatory approach whereby medicinal product advertising complaints as reported by external stakeholders are assessed and investigated in detail for purposes of verifying claims of breaches to the Advertising Regulations. Over 2008, three advertising complaints were registered with the Medicines Authority. Following assessment, breaches to the legislation were identified in relation to all three reports. In one of these cases, Article 99 of the Medicines Act 2003 was enforced with the entailing relevant legal breach penalty according to Legal Notice 264 of 2006. Another case remains pending and is subject to criminal investigation by the Commissioner of Police.

Control of advertising material is also implemented via the *ad hoc* selection and investigation of local advertisements as presented within the major media formats. Over 2008, three advertisements were assessed via this monitoring procedure.

The Medicines Authority is also responsible for providing information to stakeholders and public entities (such as MAH representatives and local public broadcasting stations) on appropriate advertising methods. In this respect, over 2008 the Medicines Authority handled nineteen (19) requests for provision of further information and/or clarifications on the advertising and promotion of medicinal products.

Picture 1: The ceremony at the start of the Twinning project with The Netherlands

Picture 2: The ceremony for the closing of the Twinning project between The Netherlands and Malta showing Hon. Minister John Dalli giving out the certificate to the participants.