ANNUAL REPORT 2006

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1.0 Executive Summary

The PMA/MA project was the major priority of 2006 and this year saw the project's concluding phases. 2006 also saw the first applications being submitted under article 126a of Directive 2001/83/EC as amended by Directive 2004/27/EC. The Inspectorate and Enforcement Directorate continued carrying out inspections of wholesale dealers and manufacturing premises and there have been an increase in the applications for partial manufacturers. Importantly there was the Canadian Audit. The Post-Licensing Directorate continued its activities in the various fields that fall within its remit and started transmitting Adverse Events into the Eudravigilance database.

A lot of time and effort was expended on the Quality Management System of the Authority during 2006 to continue the progress indicated by the Benchmarking Exercise of National Competent Authorities carried out in 2005. This was done so that the results achieved by the authority compare favourably with other more established national agencies.

In 2006 the Medicines Authority started planning and preparing for commencing activities where Malta is a Reference Member State in the Mutual Recognition and Decentralised procedures the biggest challenge was in expanding the authority's human resources. Although proposals were submitted for further recruitment these were not approved by the end of the year. In line with the training needs identified by ICH Q9, the Medicines Authority started work on a Twinning Light's Project in order to obtain funds for training its technical staff in the Assessment of EU type dossiers.

In September 2006 agreement was achieved with stakeholders regarding implementation of a number of policies. Most of the fees payable to the Medicines Authority were revised.

In the October 2006, discrepancies were detected within the Department of Finance. An investigation was carried out by Internal Audit and Investigations Directorate of the Ministry of Finance and a Magistral Enquiry was initiated.

1.1 Introduction

The main objectives for the Medicines Authority for 2006 were:

- To maximise the public health benefits to be derived from medicines regulation by registering all pharmaceutical products on the Maltese Market a Marketing Authorisation (the PMA/MA project);
- To ensure that the provisions of the EC medicines legislation are implemented in Malta in a timely and effective manner, and operated so that the needs of patients, healthcare professionals and industry are balanced with the need to meet Community obligations (transposition of various EU Laws).
- To respond to the needs of the Ministry of Health to secure an increased supply of medicines to meet public health needs.
- To ensure that the needs of all our stakeholders are taken into account in the formulation of policy and procedures and that open and transparent relations are maintained with them.
- To ensure that the Authority has the resources in place to ensure the functions of the Agency can be carried out and the systems to ensure the good governance of the Agency, that HR and financial management standards are met, and that quality of service is monitored and improved.

2.0 Corporate Issues

2.1 Management Meetings

There were 4 management meetings held over 2006. Management meetings covered management effectiveness through objectives set from previous meetings as well as systematic reporting on performance of the Medicines Authority depending on the items on the agenda. Areas covered during management meetings included the Authority's own Quality Management System its implementation and maintenance, Management's review, communication within the authority, internal audit and corrective & preventive action.

2.1 Management Review

Management Review is one the management processes used by the Authority's top management to oversee the entire management system. This activity was conducted on 1st September, 2006 and covered all departments, personnel and subordinate processes. The Plan-Do-Check-Act approach was taken and it follows the typical process model with inputs, outputs and controls etc. This system took into account the Corrective and Preventive Action efforts put into place by the management through out the cyclic year July 2005 to July 2006 which acted as input to the Management Review. It was agreed that management review was to be done annually with the management year beginning from July to June next year.

Objectives for each process activity within the Medicines Authority are defined through the CEO's high level objectives as well as the operational plans set by the different directorates and unit. Appropriate data was gathered during the interim between Management Review 2005 and Management Review 2006. The data was analysed and condensed to present the result/performance for the period. All objectives were reviewed by management. While most of the goals were reached others were revised and set as taken from the current stand point i.e.

July 2006. Corrective action and improvement was recommended where the objective's intended goal was not meet.

2.2 Finance

In 2006 the Medicines Authority was totally responsible for the management of its funds, including the annual subvention it receives from the Ministry of Finance through the Ministry of Health, the Elderly and Community Care (MHEC). The Authority started collecting fees for manufacturing activities and also for pharmacy licences and variations.

2.3 Fees

Following the efforts made in 2005, where the Authority embarked on a consultation process to amend Legal Notice 273/03, which regulated the fees the Medicines Authority charges private stakeholders for its services, Legal Notice 315 of 2006 Marketing Authorisation (Fees) Regulations, 2006 was published. Legal Notice 315 of 2006 introduced new fees on certain activities mainly carried out by the inspectorate directorate as well as for licensing activities. Legal Notice 315 also reduced fees for variations to Marketing Authorisations.

2.4 Quality Management System

In 2006 the Authority has applied the process approach to its quality management system based on ISO 9001. These included: ISO 9001:2000 "Quality management systems – Requirements" and ISO 9004:2000 "Quality management systems – Guidelines for performance improvement"; while for internal auditing purposes the authority applied ISO 19011:2002 "Guidelines for quality and/or environmental management systems auditing". Since the Medicines Authority's quality management system is built on the model of ISO 9001 it is committed to provide its customers with the highest quality for its services. In order to ensure this, concepts of customer satisfaction and continual improvement are being incorporated within the framework of the Authority's policies and procedures. The objectives of the Medicines Authority are integrated within the Quality Manual. During 2006, the 1st issue of the Quality Manual was reviewed and was updated with changes. Sequence and interaction of the Quality Management System is represented by incorporating both the

process map method in some instances but mainly utilises the text-only description method that is Standard Operating Procedures (SOPs). There are currently 77 SOPs which are divided as follows:

- General Quality Procedures 9
- Inspectorate Procedures 25
- Enforcement Procedures 5
- Quality Defects Procedures 7
- Information Technology 4
- Pre-Licensing Procedures (excluding variations) 13
- Post-licensing Procedures (including variations) 13
- Clinical Trials 1

During 2006 there were 38 quality improvement requests.

A quality system ensures that each process is fully documented and allows for a full audit trail of all activities and ensures that each member of staff is fully accountable. Particular emphasis has been given to the quality system in 2006 in view of the Canadian audit. Most of the SOP`s are in their 4th revision status thus signifying that continual improvement is being achieved. These maturing SOP`s together with the input of historical data have addressed the points raised during audits that the system still needs to prove itself.

2.4.1 EU benchmarking exercise

One assessor actively participated in the benchmarking exercise of European agencies which is being coordinated by the EMEA and Heads of Agencies (BEMA). The assessor was team leader for a benchmarking visit to an agency carried out during February.

2.5 Audits

2.5.1 MRA audit with Health Canada

In the Mutual Recognition Agreement (MRA) between the EU and Health Canada, the latter retained the right to evaluate EU member states for the GMP compliance programme. All new EU member states thus need to be evaluated by Canada. Achievement of this status will signify that Health Canada recognises the GMP certificates issued by that country, thus

allowing EU manufacturing companies to export medicines to Canada and avoiding duplication of work and inspections. Equivalent countries will be entitled to exchange the GMP certificates with Canada.

The on-site MRA audit for Malta was conducted between the 20 November and 1 December 2006. Prior to this a lot of work had been ongoing through teleconferences and submission of extensive documentation to Canada. Very positive feedback was received from the auditor, especially in respect of the legislation, documentation and quality system. Some deficiencies were identified and these related to the training of inspectors in validation of computerized systems and inspections for laboratories. No critical issues were identified. Another area for concern was the method adopted to qualify the sampling labs. Corrective actions were taken immediately to address the issues identified and these were submitted to Canada. The final report was not received by the end of 2006.

2.5.2 Internal Audit

The second internal audit for the Inspectorate Directorate was conducted in October prior to the MRA audit. All the issues raised were addressed and feedback given to the CEO regarding the timeframes for rectification. No major issues were identified by the auditors. The internal audit for the Directorate Corporate Services was initiated and suspended before it was terminated as the Director of Corporate Services had his contract terminated.

2.6 Participation in EU and other Fora

Members of staff of the Medicines Authority participated in meetings organised by the European Medicines Agency (EMEA), the Heads of Agency Meetings, meetings organised by the EU Presidency as well as other meetings organised by the EU Council. The Authority is represented at the Head of Agency meeting and at the Management Board of EMEA by its CEO. Meetings and working parties attended regularly by staff of the authority include the Co-ordination Group for the Mutual Recognition and Decentralised Procedures (CMD), Quality Review of Documents (QRD), European Directorate for the Quality of Medicines (EDQM), Committee on Herbal Medicinal Products (HMPC), Clinical Trial Facilitation

Group (CTFG), and the CHMP working groups on quality and efficacy, the EMEA meetings pertaining to GMP and GCP. Committee for Medicinal Products for Human Use, the Pharmacovigilance Working Party, the Eudravigilance Joint Implementation Group, Clinical Trials Joint Operations Group. Other important European Presidency meetings attended include EMACOLEX, Pharmaceutical Committee meetings, Meetings for Competent Authorities on Homeopathic Medicinal Products, Ad hoc group for the development of implementing guidelines for Directive 2001/20/EC and the Working Party on Pharmaceuticals and Medical Devices.

In 2006 the Inspectorate Directorate applyied for a full membership in the Pharmaceutical Inspection Cooperation Scheme (PICS) and attended meetings organised by the European Medicines Enforcement Officers (EMEO). The remit of the EMEO is to establish a networking activity between the Enforcement units of the Competent Authorities with the primary aim to prevent and assist in the reduction of counterfeit drugs that find themselves on the markets of member states. The phenomenon of counterfeit medicines is on the increase and is of major concern for regulators responsible to ensure public health. The staff from the Medicines Authority, did not attend the meetings of the European Pharmacopoeia that are held three times yearly. However, participation in the work programme was kept ongoing through correspondence, and timely feedback to European Directorate for the Quality of Medicines (EDQM) was maintained.

The Medicines Authority applied for PICS membership in October 2006. All the necessary supporting documentation has been sent to the PICS secretariat. Sweden has been appointed as rapporteur. It is perceived that the evaluation would progress at a fast rate since the Canadian audit report would be shared. The fee for PICS membership (CHF 8100) has been paid in December.

An inspector attended for the PICS annual seminar in Germany. This year`s topic covered Quality Risk Management. This was the second year that the Medicines Authority has attended in the PICS annual seminar.

2.7 Meetings and information sessions (communication) with Third Parties as well as training activities

Various meetings have been held with the concerned internal (including the Ministry of Health, the Elderly and Community Care, other Ministries/department) and external (established bodies and associations as well as the pharmaceutical industry) stakeholders mostly (though not exclusively) with respect to the legislation review process in particular with respect to the new Marketing Authorisation Regulations and the legislation regulating the fees to be charged by the Medicines Authority. In the review of the legislation concerning marketing authorisations, more specifically the regulations concerning authorisations in accordance with article 126a of Directive 2001/83/EC, as amended, a number of meetings were held and the draft legislation reviewed several times, with the aim of removing barriers which were hindering products from being registered for the local market and consequently attempting to increase the availability of medicinal products for human use to the public.

A number of information sessions have also taken place also in the form of training activities aimed at the pharmacy profession. Staff from the Medicines Authority, in 2006, delivered a series of lectures (the programme was entitled: "Regulation of Medicines and Pharmaceutical Activities") to the members of the Malta College of Pharmacy Practice, as part of the professional development programme offered by the College to registered pharmacists (and undergraduate pharmacy students) in 2006. The sessions were very well attended and topics discussed included: Regulations pertaining to Pharmacies, Pharmaceutical Legislation, Licensing of Medicines, and Pharmaceutical Activities, Advertising of Medicinal Products for Human Use, and Adverse Drug Reactions & Pharmacovigilance. In addition members of staff were involved in lecturing for the post graduate diploma in applied chemistry at the University of Malta. The topics covered the role of the inspector, counterfeit drugs, controlled drugs and pharmaceutical activities. The Medicines Authority has already received a request from the University of Malta to give lectures for a MSc pharmacy course to be started in 2007.

Regular meetings were held with stakeholders to discuss and consult on the issue of fees, legislation and other technical issues. A number of meetings were also held with Malta Enterprise and prospective companies showing an interest to set up base in Malta. During

these meetings all the required information is provided to the companies and the system for obtaining the licences clearly explained. The Authority has also been involved in providing advice and assisting companies that are in the process of finishing their site for the start up of the manufacturing activities.

Communication with stakeholders on pharmacovigilance and other post-licensing activities was achieved through the publication of a Drug Safety Bulletin and articles in journals, through regular updating of the website and through press releases and dear healthcare professional letters, when these are considered necessary. Throughout 2006, 1 edition of the Drug Safety Bulletin was drafted. 11 circulars were issued by the Post-Licensing Directorate and 6 Dear Healthcare Professional letters were reviewed by the Medicines Authority.

2006 consolidated the official website of the Medicines Authority (launched in 2005). Importantly for stakeholders the Medicines Authority has a new search facility for medicinal products on its updated Internet site (www.medicinesauthority.gov.mt). This free search facility may be used to find the summary of product characteristics and patient information leaflet on both prescription only medicine or over the counter medications. The search function can be conducted by Product Name, Active Ingredient, Marketing Authorisation Holder or ATC code. The Medicines Authority updated website has also a dedicated section on safety concerns with respect to licensed medicinal products.

At the end of 2006 the web pages of the Medicines Authority contained 1000 summary of product characteristics and 1000 patient information leaflets. In addition, the dedicated web pages on the safety of medicinal products contained 9 Post-Licensing Updates, 24 Medicines Authority Circulars and 3 Question and Answer documents.

2.7.1 Training

Two inspectors performed a shadow GCP inspection in the UK through the Bilateral Technical Agreement (BTA) with the British High Commission in Malta. The BTA project had been initiated in 2005. Training was also provided on the aspects of design space,

counterfeit medicines, Process analytical Technology (PAT), and Risk Management. Through collaboration with the Irish (IMB) and the Italian (AIFA) Authorities two inspectors participated in shadow inspections of API manufacturing. Areas of training to be tackled next year include that in relation to computer validation and inspection of laboratories since these areas have been identified as requiring attention during the Canadian audit. In September 2006, 2 assessors attended a Pharmacokinetics training seminar in Lisbon focusing on bioequivalence issues, this is in line with the direction required to increase the technical capability of the authority to assess generic medicinal products.

2.8 Information Management System

Throughout 2006, the Information Management System department continued to develop the Medicines Authority's website making it more user friendly and adding new web pages such as the Drug Safety Bulletin and the on line search Market Authoriation functionality. Throughout the course of the year the IT Department ensured that all systems in operation within the Authority were fully functional and that downtime was kept to the barest minimum possible. The IT Manager participated in various EU fora to ensure that the Authority is kept up to date on developments in the IT sector of the European medicines regulatory system.

2.9 Personnel

Throughout 2006, there has been a decrease of two assessors from the pharmaceutical assessors complement, three case managers, one administrator, one director of corporate services (reasons explained in section 2.5.2) within the staff of the Medicines . There was also an increase of three pharmacists. The technical personnel of the Inspectorate Directorate remained stable in 2006 and consisted of a Director and five inspectors, who also perform duties as enforcement officers. A plan for recruitment to prepare for an increase of new activities was submitted to MHEC. By the end of 2006 this was not approved.

3.0 Legislation

Throughout the year the Medicines Authority was involved finalizing the drafting of legal notices to transpose new EU Directives, mainly Directive 2001/83/EC, Directive 2004/27/EC and Directive 2004/24/EC. Malta has requested a derogation on the data exclusivity period in article 10; this issue is still being discussed. Article 126(a) of Directive 2004/27/EC, was transposed in February 2006 and following discussion was implemented in the end of 2006. This activity is the result following vast discussion, where legislation was amended following consultation. Various meetings with the stakeholders concerned have been held with respect to the legislation review process in particular in relation to the Marketing Authorisation Regulations. The new Marketing Authorisation Regulations to be implemented shall include the latest revision with respect to authorisations in line with article 4(2) of the Medicines (Marketing Authorisations) Regulations in accordance with article 126(a) of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use, as amended by Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004. All documentation, application forms and guidelines prepared earlier have been revised during 2006 and published on the Medicines Authority website in preparation for the implementation which started in 2006 itself. Out of the 8 applications received in 2006, 2 authorisations in accordance with article 126a of Directive 2001/83/EC as amended, have been issued by the end of the year.

Throughout 2006, the Inspectorate and Enforcement has been very active in the review and drafting of the following legislation: L.N. 64 of 2006 - Methadone (Prescribing and Dispensing) (Revocation) Rules, 2006; L.N. 264 of 2006 - Special Procedure (Penalties in respect of the Medicines Act) Regulations, 2006; L.N. 292 of 2006 - Prescription and Dispensing Requirements Rules, 2006; L.N. 315 of 2006 - Medicines Authority (Fees) Regulations, 2006. L.N. 315 of 2006 contained an update of the fees for all activities. The process of consultation with the relevant stakeholders was again adopted in the drafting and publication of legislation. During the fourth quarter the Medicines Authority was the lead author in the drafting of regulations on the new Legal Notice of 2006 “Medicinal Products (Injunction to Advertising) Regulations, 2006”. This legislation continues to transpose Directive 2004/27/EC.

4.0 Licensing Activities 2006

4.1 Introduction

Throughout 2006, the Medicines Authority undertook numerous licensing activities: granting of authorisations and product licences through the National Procedure (which includes parallel importation, as well as authorisations in accordance with article 126(a) of Directive 2001/83/EC), clinical trial applications and various European procedures (Mutual Recognition Procedure and the Decentralised Procedure) as well as variations and renewals of market authorizations. Throughout the licensing process, an evaluation and assessment of applications is carried out. The main role of the Medicines Authority is to ensure that products being licensed to be placed on the market are of the essential quality, safety and efficacy.

4.2 Operational Plans

The operational plans set for the Licensing Activities in the beginning of 2006 had to be revised in order to reflect the changing demands of the Authorities' activities as the PMA-MA project was approaching its end as a result of the approaching end of the derogation period (31 December 2006).

4.3 Licensing

4.3.1 Marketing Authorisations

4.3.1.1 National Marketing Authorisations - PMA/MA Project

The assessment of applications for marketing authorisation received through the national procedure (PMA/MA Project) represented a major part of the workload within the Licensing Directorate. During 2006, applications for national marketing authorisations for products which were listed on the derogation list were still being received. These were being processed through the PMA/MA applications process. Marketing Authorisation Holders intending to apply for products using this procedure were required to submit the full application (all parts

of the dossier), and a Marketing Authorisation issued directly following assessment. Tables 1 and 2 present the amount of PMA and MA procedures the Authority has processed or currently is processing.

National PMA's (2006)	***Jan***	***Feb***	***Mar***	***Apr***	***May***	***Jun***	***Jul***	***Aug***	***Sep***	***Oct***	***Nov***	***Dec***
Received	0	0	4	3	1	6	10	7	6	5	2	9
Issued (cumulative)	2228	2228	2228	2228	2231	2232	2233	2246	2248	2254	2265	2273
Withdrawn/Refused	103	103	104	104	104	103	103	98	98	98	98	98
Work in Progress	15	15	18	21	21	27	36	35	39	38	29	30
TOTAL (cumulative)	**2346**	**2346**	**2350**	**2353**	**2356**	**2362**	**2372**	**2379**	**2385**	**2390**	**2392**	**2401**

Table 1. *PMA/MA applications received, in progress and PMAs issued in 2006*

National MA's (2006)	***Jan***	***Feb***	***Mar***	***Apr***	***May***	***Jun***	***Jul***	***Aug***	***Sep***	***Oct***	***Nov***	***Dec***
Received	2	1	2	0	1	5	1	0	1	0	0	1
(PMA-MA & Nationals incl. line ext.) Issued	352	365	486	606	606	606	693	774	856	923	1166	1214
Work in Progress	22	22	24	24	25	30	31	19	20	20	18	18
TOTAL	**374**	**387**	**510**	**630**	**631**	**636**	**724**	**793**	**876**	**943**	**1184**	**1232**

Table 2. *Marketing Authorisations in progress and issued to date (2006). The above data includes the PMA-MA products (on derogation list) as well as new Nationals (i.e. new national applications, as well as line extensions to products already authorised / in process of being authorised through PMA-MA process).*

4.3.1.2 National Marketing Authorisations – New National Applications

Line extension applications for products issued with a PMA-MA, have also been processed during 2006. By the end of December 2006, there were 35 line extension applications received

(line extensions to products already authorised / in process of being authorised through the PMA-MA process); to-date 18 of these have been issued with a marketing authorisation. Two new national applications have been received by the Medicines Authority, of which one marketing authorisation has been issued by the end of December 2006.

4.3.1.3 Mutual Recognition Procedure (MRP) and Decentralised Procedure (DCP) Applications

The number of applications received through the Mutual Recognition Procedure and the new Decentralised procedure has also represented a significant part of the workload within the Licensing Directorate. Tables 3, 4 and 5 present the amount of MRP and DCP procedures the Authority has reviewed processed and finalised in 2006.

EU MRP Incoming (Malta as CMS)	***Jan***	***Feb***	***Mar***	***Apr***	***May***	***Jun***	***Jul***	***Aug***	***Sep***	***Oct***	***Nov***	***Dec***
Received	2	5	8	7	2	6	12	5	4	3	7	7
Approved	67	69	79	90	90	90	96	119	119	138	138	141
Withdrawn/Refused	22	22	22	22	22	22	22	22	22	22	23	23
Work in Progress	84	87	85	81	83	89	95	77	81	65	71	75
TOTAL	**173**	**178**	**186**	**193**	**195**	**201**	**213**	**218**	**222**	**225**	**232**	**239**

Table 3. *Applications received through the European MRP, work in progress and issued (2006).*

EU MR Renewals (Malta as CMS)	***Jan***	***Feb***	***Mar***	***Apr***	***May***	***Jun***	***Jul***	***Aug***	***Sep***	***Oct***	***Nov***	***Dec***
Received	3	0	3	2	3	0	0	9	1	1	0	0
Approved	2	2	2	4	4	7	7	10	12	12	13	13
Withdrawn	0	0	0	0	0	0	0	0	0	0	0	0

Work in Progress	13	13	16	16	19	16	16	22	21	22	21	21
TOTAL	**15**	**15**	**18**	**20**	**23**	**23**	**23**	**32**	**33**	**34**	**34**	**34**

Table 4. *Renewal applications received through the European MRP, work in progress and issued (2006).*

EU DCP (Malta as CMS)	***Jan***	***Feb***	***Mar***	***Apr***	***May***	***Jun***	***Jul***	***Aug***	***Sep***	***Oct***	***Nov***	***Dec***
Received	0	2	4	0	0	4	7	13	0	4	15	12
Approved	0	0	0	0	0	0	0	0	0	2	2	4
Withdrawn	0	0	0	0	0	0	0	0	0	0	0	0
Work in Progress	1	3	7	7	7	11	18	31	31	33	48	58
TOTAL	**1**	**3**	**7**	**7**	**7**	**11**	**18**	**31**	**31**	**35**	**50**	**62**

Table 5. *Applications received through the European DCP, work in progress and issued (2006)*

4.3.1.4 Variations to Marketing Authorisations

Number and type of variations to marketing authorisations processed in 2006:

Procedure	**Number**
National Applications	278
Mutual Recognition Procedure	602
Type of variation	**Number**
Type IA	414
Type IB	241
Type II	225

4.3.1.5 Parallel Importation (PI) applications

Parallel importation is the importation from an EU Member State or a country within the EEA of a medicinal product, which is already authorised on the Maltese-market, by an importer

who is someone other than the importer, appointed by the marketing authorisation holder of the product on the Maltese-market. The medicinal product may then be parallel imported in Malta provided that the importer obtains a license to market the product. Legislation regulating parallel imports has been published in 2004, and applications for parallel importation have been received since. Table 6 presents the amount of parallel import licenses reviewed processed and issued throughout 2006.

Parallel Imports	***Jan***	***Feb***	***Mar***	***Apr***	***May***	***Jun***	***Jul***	***Aug***	***Sep***	***Oct***	***Nov***	***Dec***
Received	3	5	1	0	6	2	0	0	0	1	0	1
Issued	41	43	47	50	57	59	59	59	59	59	59	60
Work in Progress	4	7	4	1	0	0	0	0	0	1	1	1
TOTAL	**45**	**50**	**51**	**51**	**57**	**59**	**59**	**59**	**59**	**60**	**60**	**61**

Table 6. *PI applications received, work in progress and issued (2006)*

4.3.1.6 Traditional Herbal Medicinal Products and Homeopathic products

To date no applications for authorization of herbal medicinal products have been received.

4.3.1.7 Linguistic check process of centrally authorized product information

In accordance with a derogation granted to the translations of documents in Maltese published by the Commission. This process of Maltese translations was on temporary hold. Because of this derogation, Marketing Authorisation holders were not submitting Maltese translations of the Commission decisions on Centrally Authorised products. As the derogation came to an end in December 2006, in preparation for 2007, the process for linguistic check has been mapped out, and the necessary set-up implemented, including the drafting of SOPs and update of glossaries, and guidelines. The linguistic check process is aimed to start in January 2007 since the derogation on the use of the Maltese language ends in May 2007.

5.0 Inspectorate and Enforcement – Activities 2006

5.1 Inspections and Issue of Licenses for pharmaceutical activities

5.1.1 Manufacturing and Import Authorisations

During 2006 five manufacturing authorizations were issued. Two authorisations were issued to new companies manufacturing products in Malta, one for a new re-packaging site and one to a company importing medicines from third countries. The other licence was a renewal. GMP certificates were also issued. A follow up inspection was necessary in the case of two companies, one of which related on an inspection conducted in 2005. Four new applications, one for gases manufacture, another for API manufacture and two for importation are being processed following the relevant inspections conducted on site. A very high activity in the area of GMP is expected during 2007, especially in the area of re-packaging and stickering operations, and the number of manufacturing companies will more than double. Besides, the Medicines Authority has been receiving indications that a number of third country manufacturers seem to be interested in establishing a plant in Malta, meaning that third country inspections may have to be catered for in the near future. This will entail a substantial burden for the Inspectorate, which at present is not yet geared for such an eventuality. Four applications for variation of a manufacturer's licence were processed and new licenses issued within the stipulated time frame of 30 days.

5.1.2 Export Certificates

259 export certificates were issued to local manufacturing companies. Export certificates serve as a means to demonstrate that a manufacturing company has been inspected by the Competent Regulatory Authority and found to be in compliance with GMP.

5.1.3 Wholesale Dealing Authorisations

All the wholesalers due for an inspection in 2006 have been inspected (*n*=16). Two new applications for wholesale dealing were received and these were processed satisfactorily and

the licenses issued. Three licenses were issued to established wholesale dealing companies upon payment of the applicable fee. The renewal licences for the other sites have not been issued in view of the fact that the fees for the inspection activities were only approved in December. The licenses in the new EU format will be issued during 2007 when the next programme for wholesale dealer inspections is initiated. Nine companies decided not to renew their licenses and to postpone until fees were issued. There were two variations for a wholesale dealer`s license.

5.1.4 Pharmacies

The Medicines Authority was fully responsible for pharmacies during 2006 and took over the responsibility of the pharmacy roster from the Public Health Department. A project was undertaken with the Health Information Department whereby a new website, eHealth, was launched. This website contains user-friendly and up-to-date information on pharmacies and the relevant roster.

The licenses for pharmacies for the year 2006 were issued by March. This system had been introduced for the first time in 2006 with the aim of issuing pharmacy licences at the beginning of the year rather than at the end of each year, as was previous practice.

Two new applications for the localities of Nadur and Kercem, both in Gozo, were approved and the licenses issued following processing through the tripartite committee. 12 applications for transfer of pharmacy licences involving a change in licence holder were received and these were all approved. There were another two variations relating to a change in premises whilst there was one application in connection with a change in pharmacy name.

5.1.4.1 Process verbal

208 inspections of retail pharmacies were carried out for the scope of renewal of pharmacy licenses. The process includes the renewal of the process verbal. This is a process whereby pharmacies are inspected for compliance with the Medicines Act and with the standards of

Good Pharmacy Practice. An approach was taken to reinforce and sustain the standards introduced in 2005 relating to temperature control and monitoring and pest control.

5.1.4.2 Revocation of license

One pharmacy license was revoked after the pharmacy was kept closed for a very long time. This license was re-instated following *rectification* of the issues and an undertaking that the provisions of the Medicines Act will be observed. No further complaints have in fact been received following reinstatement of the license.

5.1.5 Sampling of Medicines

Sampling of sterile products was initiated in 2006 following establishment of a contract for analysis with the MHRA. A total of 14 non-sterile products and 9 sterile products were sampled. All results showed a satisfactory outcome.
The Medicines Authority participated in the annual CAP testing organized by the EDQM by sampling and testing of the product avandamet.

5.1.6 Enforcement

13 complaints were received and all of these were investigated. 3 cases lead to an enforcement action. A seizure was effected in one case. All cases, except 2, have been closed. 1 case was referred to the Pharmacy Council and another, involving medical doctors, to Director General, Health. The Medicines Authority collaborated with customs in the seizure and destruction of a counterfeit medicinal product being imported from a third country. Current collaboration is being undertaken with police, customs and the MHRA regarding importation of medicines destined for export to third countries.

5.1.7 Court cases

The Medicines Inspectors provided their services as witnesses in 3 court cases for prosecution proceedings initiated against offenders. All these cases related to pharmacies.

5.2 Other Activities

5.2.1 Inspection Review Group

5 meetings of the Inspection Review Group were held in relation to 8 cases. The remit of this group is to consider action in cases of critical deficiencies and serious non-compliance.

5.2.2 Batch Defect Reports

During this year the Inspectorate received and processed 51 rapid alerts in respect of product quality defects. 5 batch recalls were effected following these reports. There was also one voluntary recall. No batch recalls were effected in relation to locally manufactured products.

5.2.3 Qualified Persons' Assessment

QP interviews were held in January and November. 6 applications were received and the applicants were interviewed by a panel from the Medicines Authority. 4 applicants were successful and have been accepted as QP`s on the respective manufacturing authorisation.

6.0 Post-Licensing – Activities 2006

6.1 Introduction

The Post-Licensing Activities that the Medicines Authority that is responsible for include pharmacovigilance, haemovigilance, processing of variations to marketing authorisations, as well as the regulation of promotional material on medicinal products for human use. The overall objective in 2006 was to consolidate the responsibility which the Authority has for the implementation and enforcement of relevant legislation with respect to the regulation of medicinal products for human use and pharmaceutical activities.

Work in 2006 focused on finalising the following legislation: "Medicinal Products (Injunction to Advertising) Regulations, 2006". These regulations affectively transpose Directive 2004/27/EC amending Directive 2001/83/EC, processing of variations, advertising complaints and pharmacovigilance.

6.2 Pharmacovigilance activity

The activity of pharmacovigilance, functioning within the Medicines Authority, was developed in line with the regulations entered in force throughout 2005, namely Legal Notice 22 of 2004 which transposes Directive 2001/83/EC Title IX.

In 2006, pharmacovigilance activity involved the management of the following drug safety reports/requests:

31 were Individual Case Safety Reports (ICSRs) from healthcare professionals in Malta

56 CIOMS forms of Adverse Drug Reactions ADRs occurring locally forwarded by industry

44 Non-Urgent Information Requests

5 Rapid Alerts

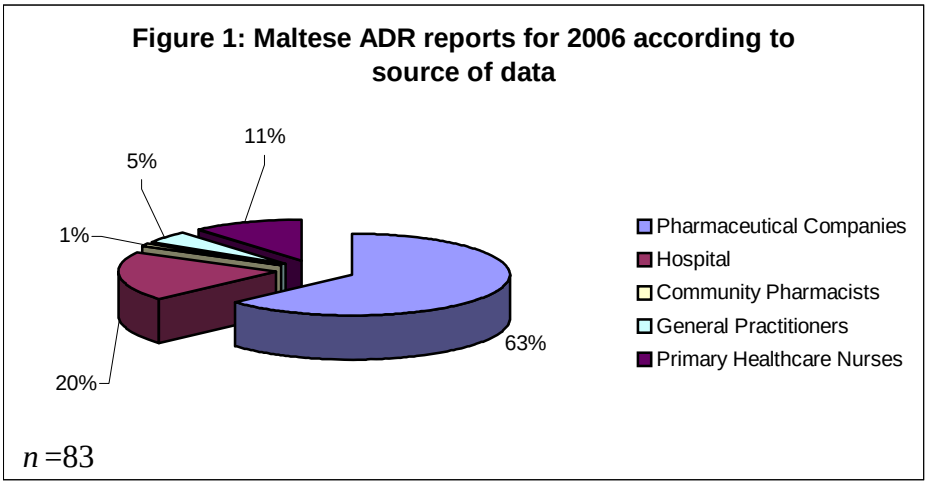
Additional information was requested on 13 ADRs. These include 3 follow-up letters.

Measures taken to encourage ADR reporting by practicing Healthcare Professionals included the introduction of the self addressed ADR reporting form and specific lectures at the College of Pharmacy Practice.

6.2.1 Source of Data

Analysis of the ADRs received showed that the pharmaceutical industry is responsible for most ADR reports submitted in 2006 to the Medicines Authority (Figure 1). Healthcare Professionals (doctors, pharmacists and nurses) also submitted ADR reports to the Medicines Authority.

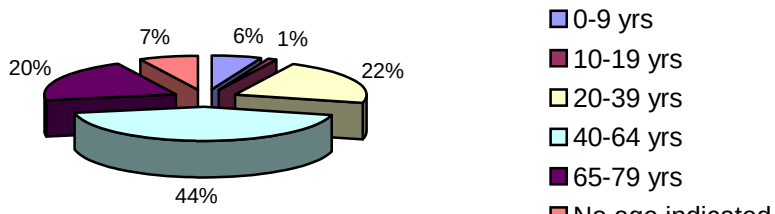
Figure 1: Maltese ADR reports for 2006 according to source of data



6.2.2 Age of Patient

Analysis of ADRs by age of patient (Figure 2), shows that the most common patient age group experiencing ADRs is between 40 to 64 years (*n*= 36), followed by 20 to 39 (*n*=18) and 65 to 79 years (*n*= 17).

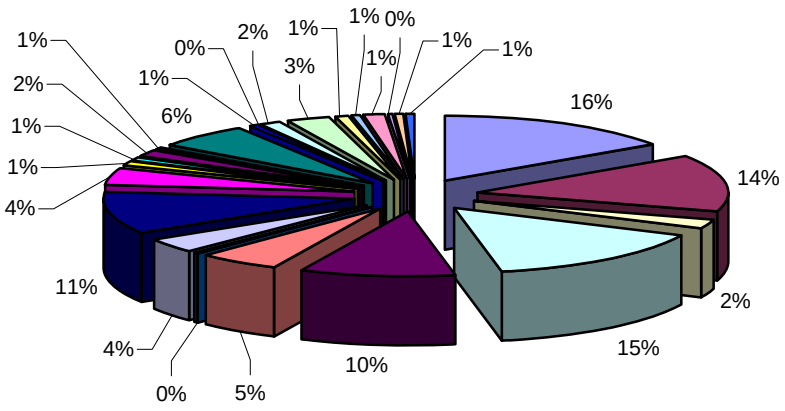
Figure 2: Maltese ADR reports for 2004 - 2006 according to age of the patient



6.2.3 Body System

Body as a whole - general disorders (*n*= 52) is the system-organ class for which ADRs are most reported followed by the Skin and appendages disorders (*n*= 50) and Gastro-intestinal disorders (*n*= 47) (Figure 3).

Figure 3: Maltese ADRs for 2004 - 2006 according to System Organ class

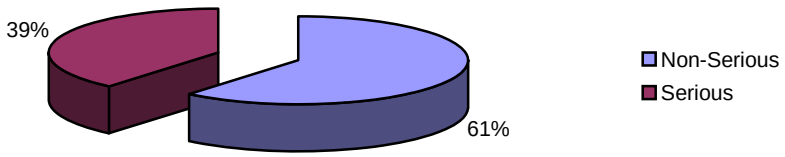


- Body as a whole - general disorders
- Gastro-intestinal disorders
- Vision Disorders
- Skin and appendages disorders
- Central and Peripheral nervous system disorders
- Application site disorders
- Special senses other, disorders
- Cardiovascular Disorders, general
- Psychiatric disorders
- Musculoskeletal system disorders
- Urinary system disorders
- Neoplasms
- Vascular (extracardiac) disorders
- Liver and biliary system disorders
- Metabolic & nutritional disorders
- Endocrine disorders
- Myoendopericardial & valve disorders
- Heartrate & rhythm disorders
- Respiratory system disorders
- Red blood cell disorders
- Platelet, bleeding & clotting disorders
- Urinary system disorders
- Reproductive disorders, female
- Reproductive disorders, male
- Resistance mechanisms disorders

6.2.4 Seriousness

Over half (61%; *n*= 186) of the ADRs reported were considered as non-serious (Figure 4). The criteria for seriousness included fatal, life threatening, caused or prolonged hospitalisation, caused congenital abnormality or caused disability or incapacity.

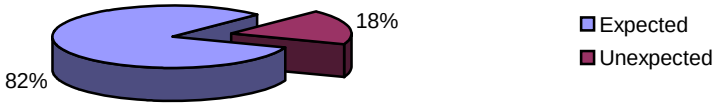
Figure 4: Seriousness of Maltese ADRs reported in 2004-2006



6.2.5 Expectedness

The majority (82%; *n*= 249) of ADRs reported were expected and thus already listed in the summary of product characteristics of the medicinal product (Figure 5).

Figure 5: Expectedness of Maltese ADRs reported in 2004-2006



6.2.6 Queries

A total of 40 queries were addressed to the Pharmacovigilance section during the second half of 2006. One area which was the subject of many queries was the transmission of ADRs through the Eudravigilance (Figure 6). This is directly attributable to queries from industry, as may be seen in Figure 7.

Figure 6: Query subjects in 2006

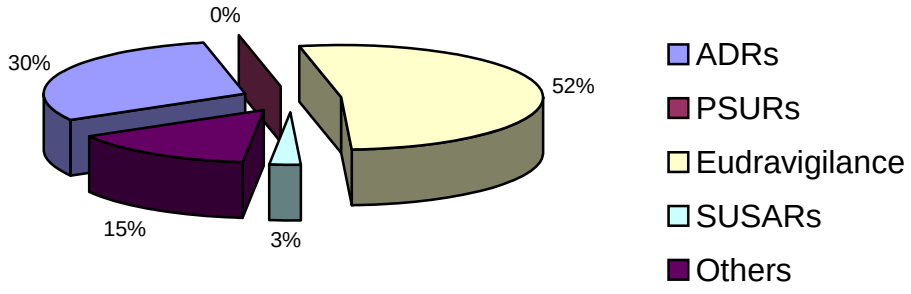
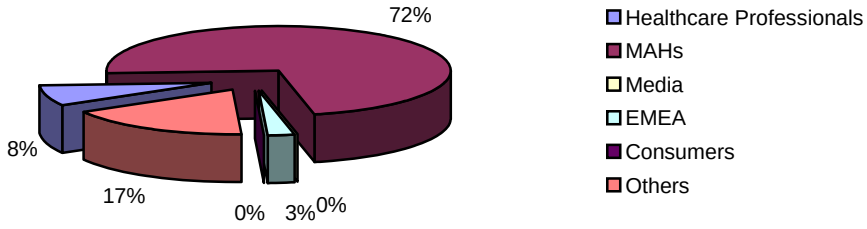


Figure 7: Maltese ADR queries for 2006 according to source of data



6.3 International Relations on pharmacovigilance

The establishment of the ADR reporting system by the Medicines Authority and the participation of Healthcare Professionals, through reporting of ADRs encountered during their practice has enabled Malta to comply with existing EU regulations. Besides, the transmission of 150 reports to the WHO Collaborating Centre for International Drug Monitoring, the Medicines Authority has renewed in 2006 its full membership for Malta in the WHO programme.

7.0 Other Additional Activities

7.1 Borderline Classification Committee

During 2006 the Borderline Classification Committee held 6 internal meetings. Two meetings were held with Malta Standards Authority (MSA) to discuss procedures regarding products containing herbal ingredients and vitamin and mineral products and also to discuss products such as appetite suppressants, gym products and enquiries from other member states. These meetings are being held following an agreement with MSA to discuss issues common to both Authorities, including products that are borderline between medicinal products and food supplements, cosmetics or medical devices.

Products were referred to the BCC mainly from local companies, other products from the Malta Standards Authority (MSA), the Government Pharmaceutical Services (GPS), and from Competent Authorities in other Member States. During 2006 the Borderline Classification Committee reviewed a total of 316 classification requests. A breakdown of activities is as follows:

- 9 requests concerned products that were classified as medicinal products
- 37 requests concerned products that were classified as not medicinal products
- 244 requests concerned products that were classified as products containing herbal ingredients may be considered to be traditional herbal medicinal products (THMP) in accordance with Directive 2004/24/EC. In the absence of safety concerns, the Medicines Authority did not object to the marketing of these products, provided that no medicinal claims are made regarding the products.
- 26 decisions are still pending due to various reasons. For example a number of products are being discussed with the Malta Standards Authority who in turn also liaises with the Food Safety Commission. In other cases further information is awaited from other Competent Authorities in other Member States or from applicants.

The BCC constantly consults with other bodies both locally and abroad in order to obtain the opinion of experts in other areas such as on medical devices, biocides and herbal products. The opinion of the UK Competent Authority was also sought on a number of products.

7.2 Clinical Trials

6 Clinical Trials were submitted to the Medicines Authority. 4 were approved in 2006 and two were currently undergoing assessment. 5 amendments to trials which are being conducted in Malta were also received. 3 were approved and 2 were currently undergoing assessment.

7.2.1 Queries

A total of 53 queries on clinical trials were reviewed during the second half of 2006. CROs and/or industry raised the greatest amount of queries.

Figure 8: CT queries for 2006 according to source of data

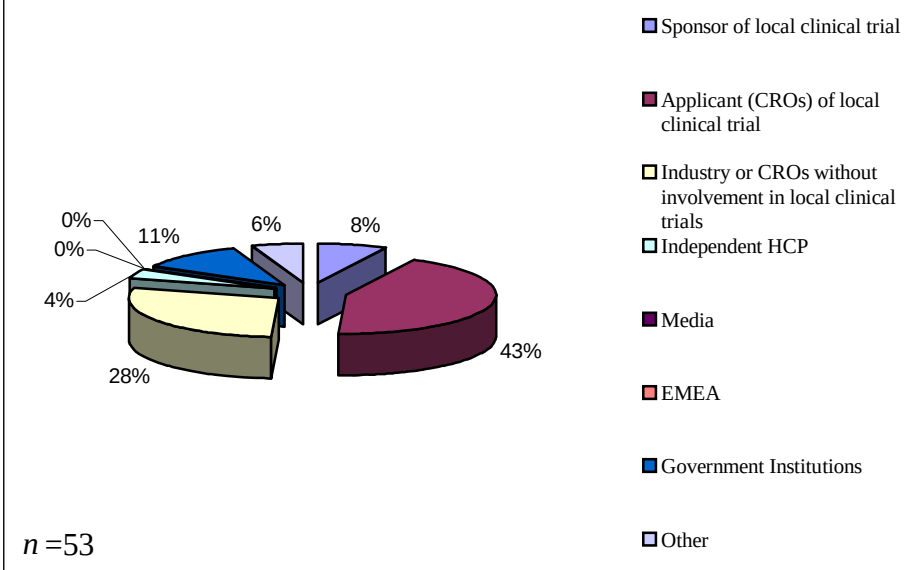
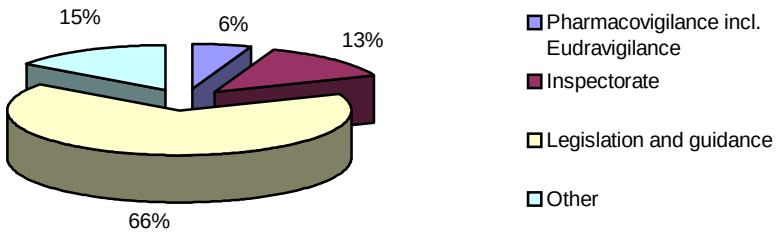


Figure 9: Subject of queries in 2006



n =53

7.3 Regulation of advertising and promotional material

In 2006 the Authority handled forty-seven cases related to advertising which included:

- Addressing 21 formal queries from a variety of sources on implementation of the advertising regulations
- Investigating and evaluating 9 complaints from stakeholders
- Advising on 4 advertisements forwarded to the Authority prior to publication
- Reviewing 13 advertisements forwarded to the Authority for our advice as part of the monitoring system

In addition, a presentation on the regulation and monitoring of advertising was delivered to pharmacists.

7.4 other matters

A local ADR Database (MDIS) has been maintained in order to record data from locally occurring 72 ADR reactions reported to the Medicines Authority in 2006. Three staff members have been trained in 2006 on ADR data inputting into the European Network, namely the Eudravigilance Web-trader function. 1 Eudravigilance Joint Implementation Group meeting was attended in 2006.